SYNTHETIC STUDIES ON GIBBERELLINS

THESIS

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Glasgow for the degree of
Doctor of Philosophy

by

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I benevolently accept this opportunity to state my appreciation of Dr. A. J. Baker, who has been a veritable, indefatigable paragon, always altruistic and profuse when called upon for proffered assistance, and Dr. J. Carnduff, my mentor throughout my undergraduate research.

I would also like to express my gratitude to other members of staff, research colleagues, technical staff, especially Jean, Margaret and Betty for services rendered, and Prof. G. W. Kirby for the award of the "James Fleming Scholarship" for the duration of my studies.

I am also indebted to the late Ronnie Van Zant, who's music has stimulated me in moments of depression.

Finally I would like to mention my mother, Christina, for making it all possible.

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SYNTHETIC STUDIES ON GIBBERELLINS.

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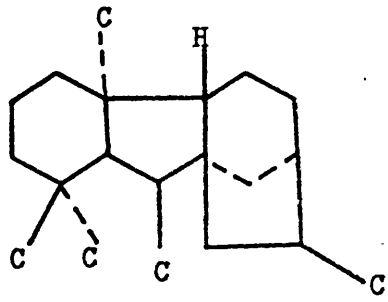
SUMMARY.

Based upon the serendipitous conversion of 5-carbomethoxy-2-(p-methoxyphenyl)-cyclohexane-1-carboxylic acid into endo-2-(p-methoxyphenyl)-cyclohexane-cis-1,5-dicarboxylic acid anhydride, a stereospecific synthesis of 1,2,3,4,4a(βH),9a(βH)-hexahydro-7-methoxy-9-oxofluorene-2-carboxylic acid has been achieved in excellent yield, originating from the regiospecific and stereoselective Diels Alder cyclisation between acrylyl chloride and 5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoyl chloride. The Diels Alder reaction between related dienes and dienophiles was also investigated.

A detailed investigation of the intramolecular Dieckmann cyclisation of methyl (1,2,3,4,4a(βH),9a-hexahydro-2-carbomethoxy-7-methoxy-9-oxofluorenyl-9aβ)-acetate and of its 9-desoxy and 9α-hydroxy derivatives as a route to 3-methoxy-6,16-dioxo-9(βH)-gibb-A-triene suggests that strain factors are the cause of failure of this cyclisation.

3-methoxy-16-oxogibba-1(10),2,4,9(11)-tetraene was obtained by acid catalysed cyclisation of the olefinic diazo ketone, 1,2,3,4,4a(βH)-tetrahydro-$\Delta^{9,11}$-2-diazoacyl-7-methoxyfluorene. A keto-carbenoid C-H insertion reaction applied to the corresponding hexahydro and 9α-hydroxy-hexahydro derivatives failed to yield any tetracyclic material.

An attempt to extend the Parham hydrofluorene synthesis failed at an early stage when 2-bromo-5-methoxybenzyl alcohol, or its 1-alkoxy-1-ethoxyethane acetal derivative failed to undergo electrophilic halogen exchange. A similar lack of success was experienced with the corresponding Grignard reagent.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C
C

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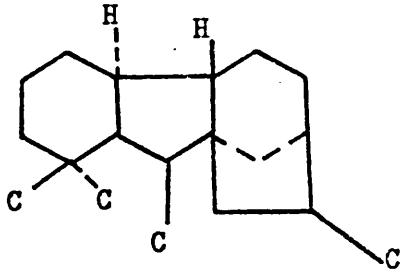
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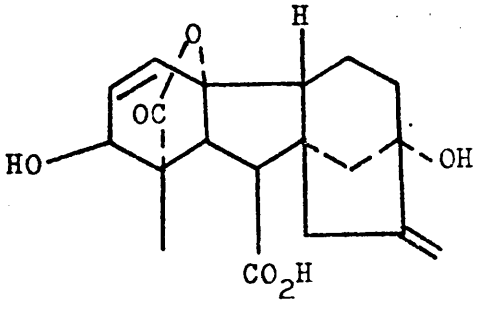
(2)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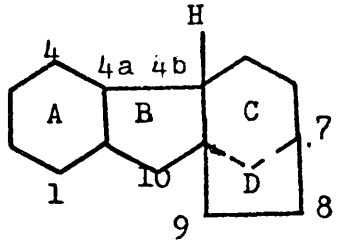
(3)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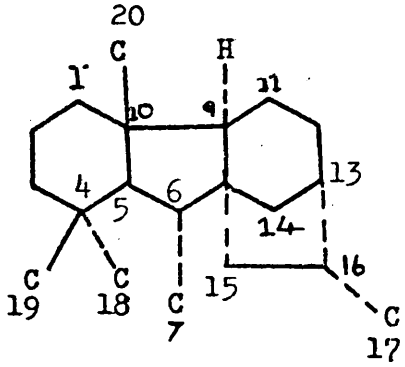
(4)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C
17

(5)

INTRODUCTION

When that ray of sunshine's overdue,
When the dies are down on a losing streak,
When lady luck's got nothing new,
When your mind is willing but your heart is weak,
You've got to keep on trying.
D. Cousins.

Interest in the chemistry of gibberellins started in 1938 when a group of Japanese researchers[1,2] first isolated a crystalline plant growth regulator from cell-free extracts of the fungus gibberella fujikoroi during their studies into a soil borne affliction of rice called Bakanie disease. For want of a better name, the solid was classified as being a gibberellin. Unfortunately, advances in gibberellin chemistry remained fairly indolent until the first gibberellin was obtained in a pure form by the British pairing of Cross and Curtis[3] who reisolated gibberellic acid in 1954. Until then most of the Japanese work was of doubtful value in view of the uncertainty concerning the composition of the gibberellins, leading to the incongruous situation of rival chemists isolating these mould metabolites under identical conditions to find the products differing in physical and chemical properties. In one instance Stodola[4] obtained a metabolite and named it gibberellin X before tentatively labelling it correctly as allogibberic acid. Final confirmation concerning the structure and absolute stereochemistry of the gibberellins was not achieved until Scott and Sim[5] carried out an x-ray structure analysis and circular dichroism measurements on a gibberellic acid derivative in this department in 1962.

The gibberellins, which are diterpenoid acids, are endogenous plant hormones associated with the regulation of plant growth[6] and can be divided into two groups, namely, the C_{20}-(1) and the C_{19}-(2) gibberellins. The structure of all known gibberellins has been assigned by interconversion and correlation with the parent acid (3).

Formerly, the gibberellins, their derivatives and degradation products were named as derivatives of the

hypothetical gibbane (4) and numbered as shown. However, a more recent convention, based upon the hypothetical gibberellane (5), has been proposed by Rowe[7] and was first adopted by MacMillan[8]. Although the use of gibberellane nomenclature is often cumbersome when C_7, C_{17}, C_{18}, C_{19}, C_{20} elements are absent, it maintains the correlation with diterpenoid nomenclature. In this thesis gibbane nomenclature and gibberellane numbering will be used.

Due to their remarkable biological activity, the synthesis of gibberellins is of pivotal importance. However, since these molecules possess inordinate structural and stereochemical complexity, their synthesis tend to be esoteric, containing a myriad of steps which reduce their commercial viability compared to the plant extracted gibberellic acid which retails around £6 per gram. This leaves the way open for the field of partial synthesis which has attracted interest at the expense of total synthesis in recent years.

This introduction will primarily cover the synthesised of gibberellins and related synthons in the last four years; the biosynthesis has been comprehensively reviewed by MacMillan[6,9] and is not discussed here.

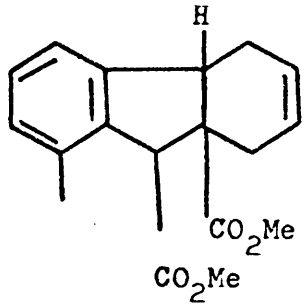
Synthetic studies directed towards the gibberellins can be considered under three main categories:

a) Synthesis based on the prior construction of a hydrofluorene.
b) Partial synthesis.
c) Synthesis with the prior functionalisation of the CD ring system.

a) <u>Hydrofluorene derived routes.</u>

Stereochemically, the least demanding route to the gibbane skeleton lies in the construction of a suitably functionalised hydrofluorene in which either ring A or ring C is in the protected form of being aromatic, thus reducing the molecule's vulnerability to attack while the other functionalities are formed.

One of the leading authorities in this field is House, who, in a series of papers investigating synthetic routes to gibberellins and related compounds, used this



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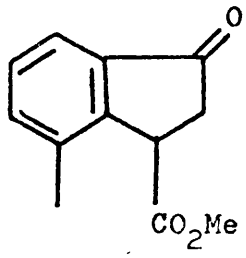

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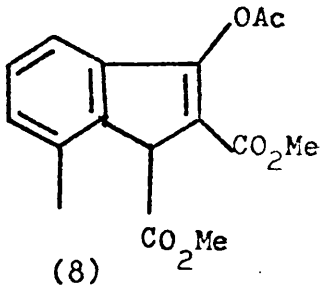

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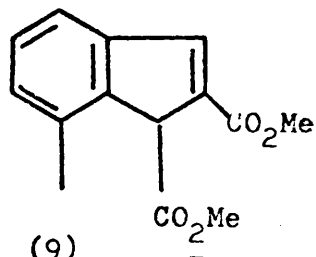

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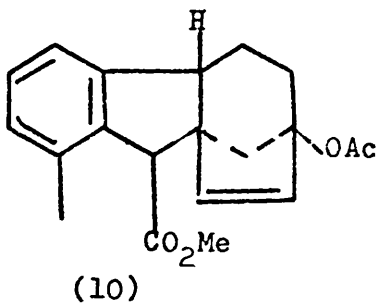

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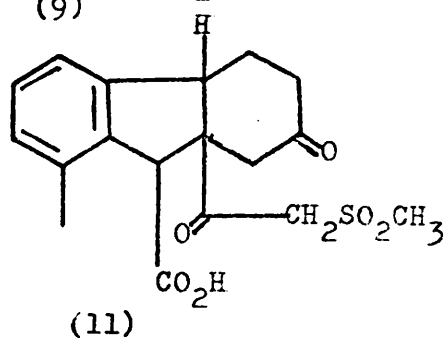

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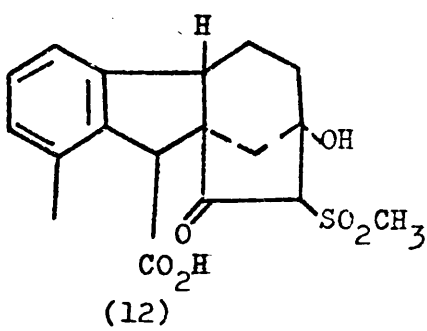

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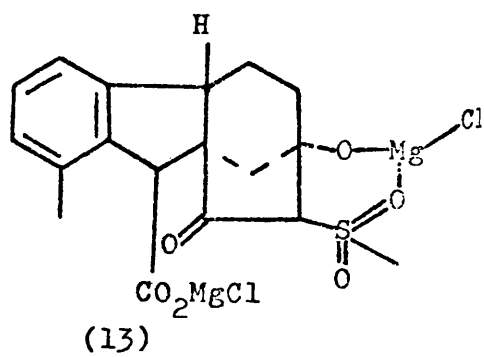

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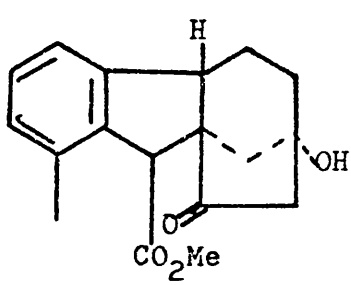

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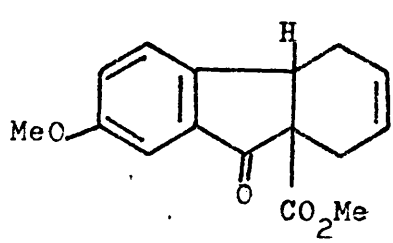

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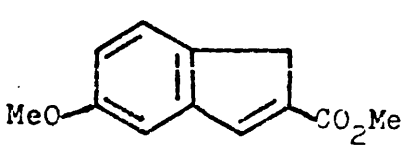

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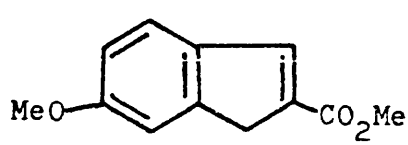
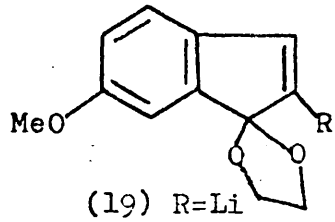


(16)

method in his synthesis of the epiallogibberic acid precursor[10] (6). The route chosen involved the formation of the indanone (7), prepared from o-tolualdehyde by standard procedures, which was then carbomethoxylated using dimethyl carbonate and sodium hydride and converted to the related enol acetate (8) by the reaction with acetic anhydride and perchloric acid. Hydrogenation, followed by acid catalysed elimination of acetic acid yielded the diester (9) which afforded the desired adduct (6), following a Diels Alder reaction with butadiene at elevated temperatures.

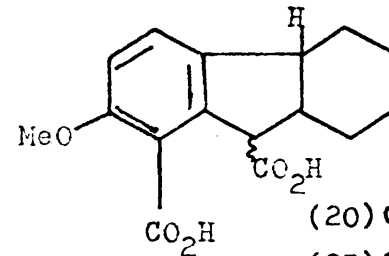
Having attained his initial goal, the second intermediate was then pursued. The compound chosen was the ester[11] (10) which had the appropriate functionality and stereochemistry to serve as a precursor for epiallogibberic acid. The successful path involved the saponification of diester (6) followed by iodolactonisation, reductive removal of iodide by tri-n-butyltin hydride and then treatment with an equimolar mixture of dimethyl sulphoxide and methyllithium, followed by Jones oxidation. This produced the intermediate (11) which underwent an intramolecular aldol condensation to afford the sulphone (12). This reaction was unfavourable in polar, protic solvents but was forced to completion by the formation of a covalent magnesium alkoxide (13) in nonpolar, aprotic solvents by treatment of (11) with two equivalents of t-butylmagnesium chloride. Reaction of the aldol adduct (12) with diazomethane, followed by acid catalysed hydrolysis and reductive clevage with aluminium amalgam, formed the hydroxy ketone (14) which was converted to the acetoxy olefin by the scheme devised by Nagata[12] involving the formation of the acetate, reduction with sodium borohydride, quenching of the alkoxide with methylsulphonyl chloride and then refluxing the product in collidine.

In conjunction with this work, and noting the high degree of stereoselectivity for the Diels Alder reaction, House[13] synthesised the hydrofluorenone (15). Previous studies of the reaction between butadiene and the unsaturated ester (16)[14,15] established that the rather vigorous conditions required for a successful reaction resulted in the concurrent isomerisation of the double bond to afford the olefin (17)



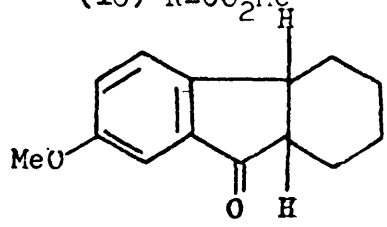
(19) R=Li

(18) R=CO_2Me



(20) α-CO_2H

(25) β-CO_2H



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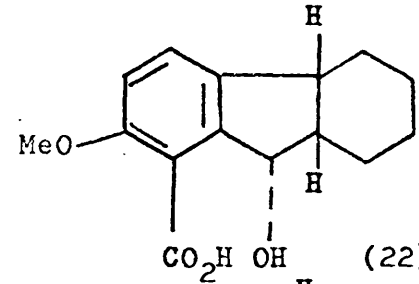

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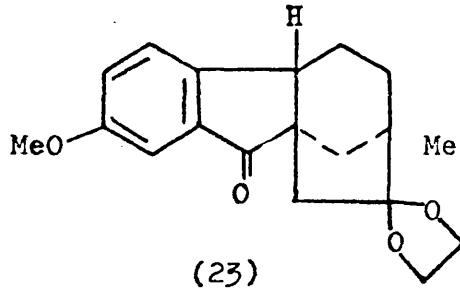

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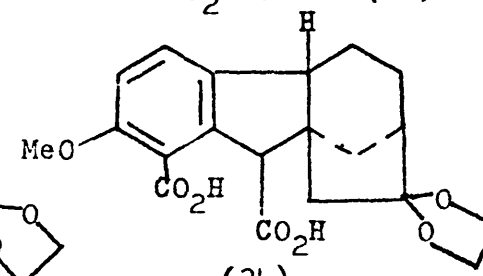

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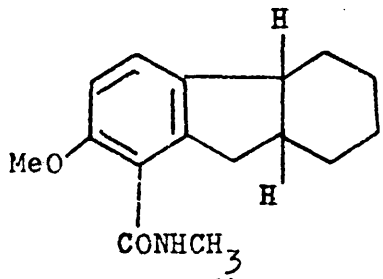

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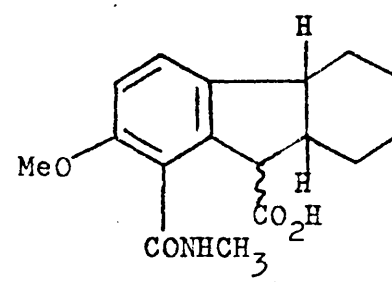

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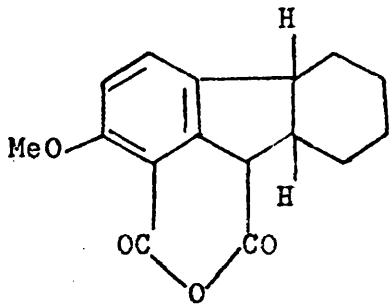

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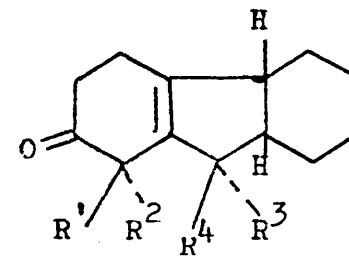


(29) R=Me, R^4=H, R^2=R^3=CO_2H

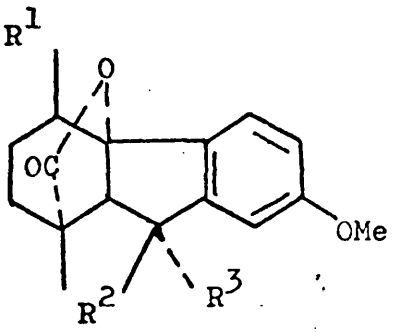
(30) R^2=Me, R^3=H, R'=R^4=CO_2H

The problem was overcome by using the non-isomerisable indenone ketal (18), prepared from 7-methoxyindan-1-one. Monobromination, ketalisation and exchange with n-butyllithium on the indanone produced the β-alkoxy organolithium compound (19) which was unusually stable due to the fact that elimination of lithium alkoxide would produce a highly strained, cyclic allene. Carbonation of the lithio derivative, followed by esterification, produced the indene ketal (18), Diels Alder reaction of which, at relatively low temperatures, with butadiene, followed by acid hydrolysis, produced the desired fluorene (15).

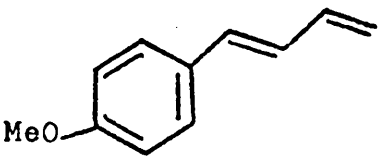
Continuing his study on the 7-methoxyhexahydrofluorene system, House[16] described an elegant synthesis of the diacid (20). The known ketone (21) was reduced to the corresponding α-alcohol, which was regioselectively carboxylated, using n-butyllithium, sodium-t-butoxide and carbon dioxide to yield the acid (22). A similar sequence was successfully applied to the gibbane (23) by Baker[17] to afford the acid (24).

House[18,19] has now managed to synthesise the β-epimer(25) of the diacid (22). The amide (26), obtained from the hydroxy acid (22) by hydrogenolysis, followed by reaction of the corresponding acid chloride with methylamine, was converted to an easily seperable mixture of amide-acids (27) by the reaction with carbon dioxide and n-butyllithium as before. Hydrolysis of the β-epimer, via its N-nitroso analogue, with dilute sodium hydroxide, produced the β-diacid (25). In this investigation it was also found that the less thermodynamically stable α-epimer could be converted to the more stable β-diacid via the formation of the anhydride (28), which was formed on treatment of the diacid with dicyclohexylcarbodiimide and subsequent aqueous hydrolysis. In connection with the modification of ring A, reductive methylation of each epimer (20) and (25) seperately with lithium, liquid ammonia and methyl iodide produced the keto-diacids (29) and (30) respectively.

Utilising the hydrofluorene approach, Nakanishi[20] prepared the lactone (31). Diels Alder addition of ethyl-3,3-dicyano-2-methylprop-2-enoate, readily available from the Knoevenagel condensation between ethyl pyruvate and



(31) R^1=OAc, R^2R^3=o
(35) R^1=OH, R^2=CO_2H, R^3=H
(36) R^1=$OSiMe_3$, R^2R^3=O
(37) R^1=$OSiMe_3$, R^2R^3=CH_2—O
(38) R^1=$OSiMe_3$, R^2=CHO, R^3=H
(39) R^1=OH, R^2=CO_2Me, R^3=H
(40) R^1=OH, R^3=H, R^2=



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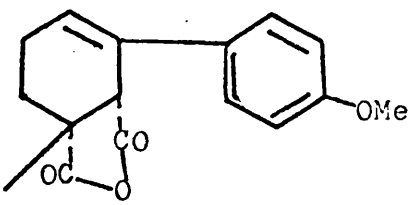

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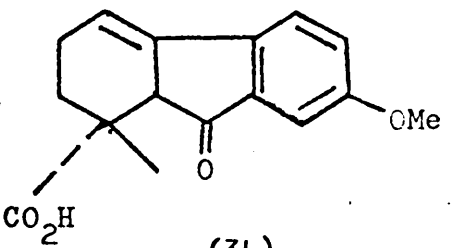

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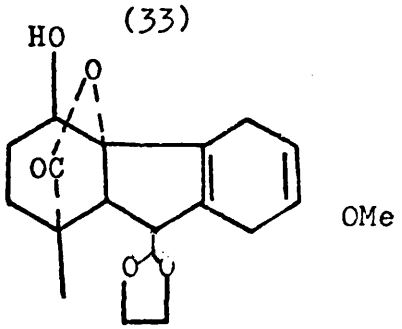

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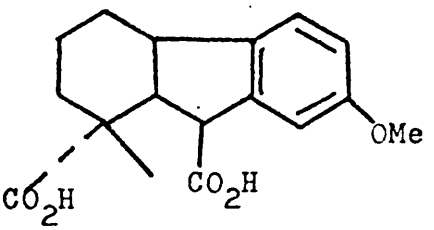

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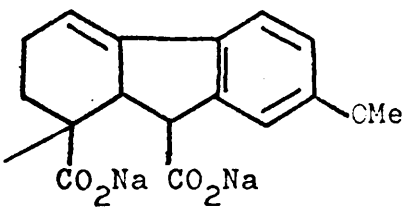

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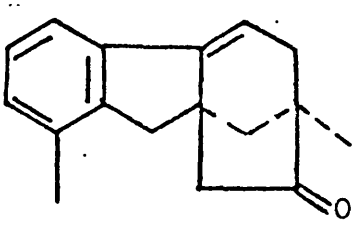
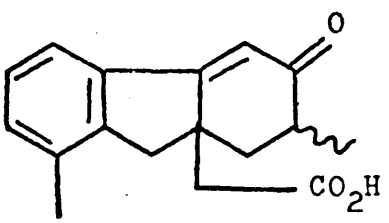
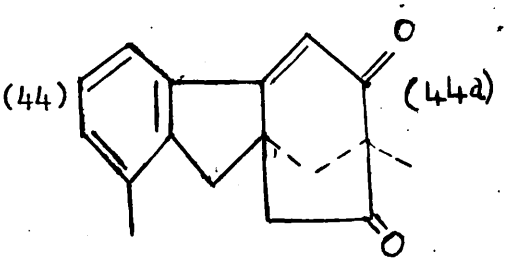


GIBBERONE





(44)

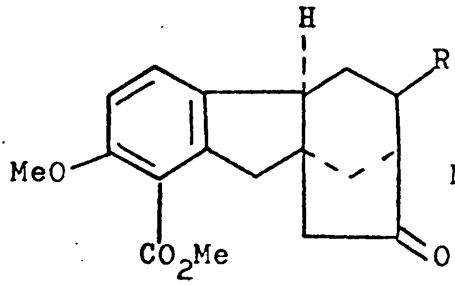
(44a)

malononitrile, and the diene (32), followed by base hydrolysis and concomitant shift of the double bond, decarboxylation and dehydration afforded the anhydride (33). Treatment with aluminium chloride gave the hydrofluorenone (34) which was readily converted to the lactone (31) by hydroxy lactonisation with p-nitroperbenzoic acid followed by acetylisation. This approach was extended[21] to produce the ring B carboxylic acid (35) stereosellectively from the reaction of the corresponding trimethylsilyl ether (36) with dimethylsulphoniummethylide in a binary solution of tetrahydrofuran and hexamethylphosphorus triamide to afford the β-epoxide (37). Rearrangement of the epoxide with boron trifluoride etherate afforded the β-aldehyde (38) exclusively. Mild Jones oxidation, subsequent methylation and treatment with p-toluenesulphonic acid yielded the 9β-methoxy carbonyl derivative (39) in 90% overall yield.

Having modified rings A and B, ring C was functionalised by Yamada[22]. Starting from the ketal (40), saponification, followed by Birch reduction and acetic acid assisted lactonisation produced the diene acetal (41), a molecule which shows appreciable possibilities in the future formation of ring D. Curiously, if Birch reduction was applied directly to the lactone acid (35), then ring C remained aromatic and high yields of diacid (42) were obtained, possibly explaned by the formation of a styrene type intermediate (43) which might be formed by the initial hydrogenolysis of the C-O bond at the benzylic position. In the previous case, clevage of the C-O bond at the benzylic position was presumably prevented by the conversion of the free hydroxyl group to an alkoxide ion during the reaction.

Loewenthal[23] and Raphael[24] independently synthesised gibberone, a degradation product of gibberellic acid (3). Loewenthal's method consisted of the annelation of a suitably substituted indanone to give the tricyclic acid (44) which cyclised with the correct stereochemistry on boron trifluoride etherate treatment to give (44a).

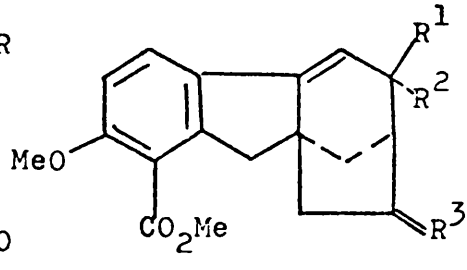
Since his earlier success, Loewenthal has tried to synthesise gibberellin A4 and suitable tetracyclic synthons based on his gibberone pathway. He formed the tetracyclic ketones[25] (45) and (46), with the former having the unnatural C-9 configuration. The route followed involved the formylation



(45) R=H

(52) R=OH

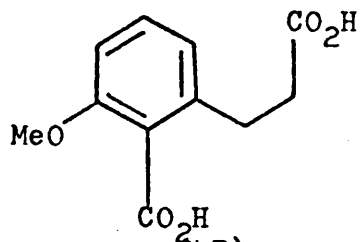
(53) R=OCOC$_6$H$_4$-p-Me (S)



(51) R^1=R^2=H, R^3=O

(46) R^1R^2=O=R^3

(54) R^1=R^2=H, R^3= 



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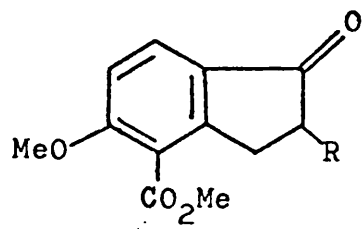
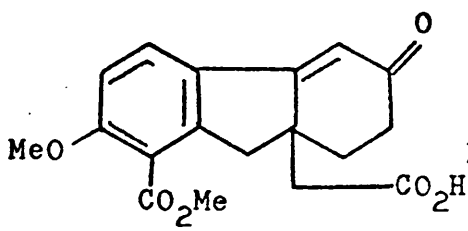


(48) R=H

(49) R=CH$_2$CO$_2$Me



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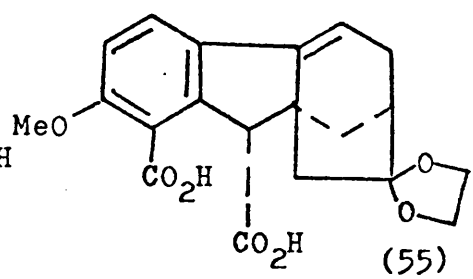

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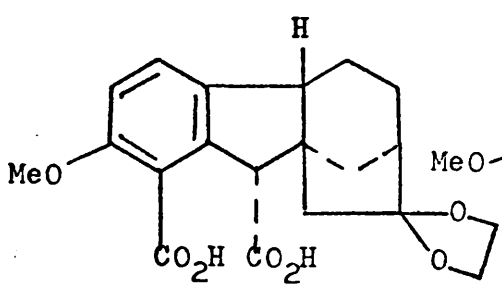

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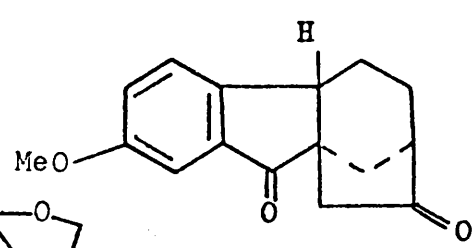

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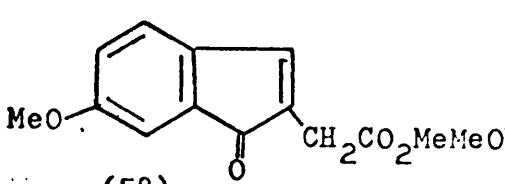

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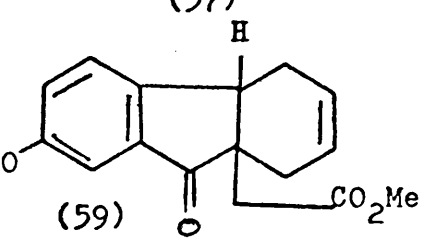

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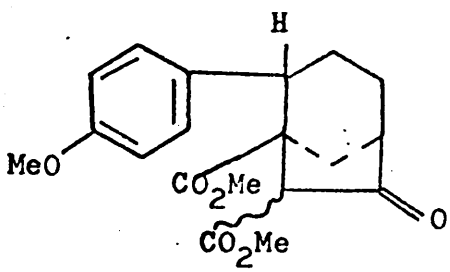
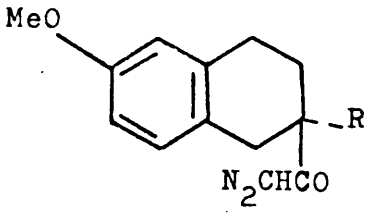


(60)

of 7-methoxyindan-1-one and subsequent treatment with hydrogen peroxide in refluxing t-butanol to give the dicarboxylic acid (47). The half ester was treated with oxalyl chloride and then aluminium chloride to afford, after remethylation, the keto-ester (48). Acid catalysed aldol condensation with n-butyl-glyoxalate, followed by catalytic hydrogenation and methanolysis, led to the diester (49) in 76% overall yield. Treatment of the diester with methyl vinyl ketone in methanolic sodium methoxide gave the half ester (50) which was cyclised with trifluoroacetic anhydride to the diketo-ester (46), which afforded the ketone (45) after a lengthy process. Unfortunately this synthon showed no biological gibberellin-like activity. To combat this he[26] synthesised the ketone (51) by treatment of diketone (46) with freshly prepared palladium hydroxide in methanol to yield the hydroxy ketone (52) which was dehydrated by pyrolysing the derived p-tolylthiocarbonate (53) at 250° and 0·1mm Hg. The resulting enone was refluxed in p-xylene with palladium to afford the desired isomeric enone (51), catalytic hydrogenation of which produced the unnatural BC ring junction ketone (45). The final breakthrough occurred[27] when ring B was functionalised by treatment of the ketal (54) with N-cyclohexyl-N-t-butylamide and carbon dioxide to afford the diacid (55) stereoselectively. Hydrogenation of the diacid (55) gave the natural BC ring linkage (56).

In a novel procedure, Martens[28] produced the diketone (57) which has the desired cis-fused BC ring junction. The starting material was the indenone (58), Diels Alder reaction of which, with butadiene, followed by base hydrolysis produced the hydrofluorene (59) in high yield. Polyphosphoric acid treatment, followed by catalytic hydrogenation, afforded the diketone (57). This provided an alternative route to the diketone from that executed earlier by Baker[29], who, starting from the Diels Alder cyclisation between itaconic acid and methyl-5-(p-methoxyphenyl)-trans,trans-2,4-dienoate, followed by catalytic hydrogenation, esterification with diazomethane and Dieckmann cyclisation, produced the keto-diester (60). Base hydrolysis of the decarboxylated keto-diester, followed by the interconversion of the resulting acid to its acid chloride produced, after an intramolecular Friedel Crafts acylation,



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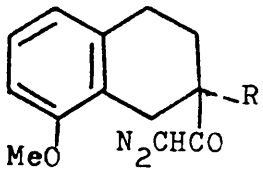

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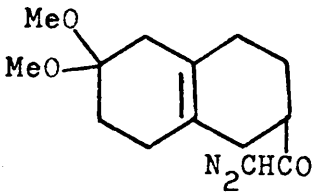

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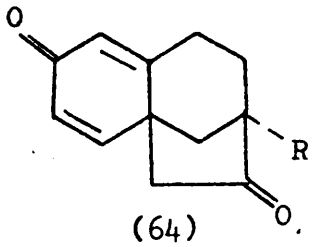

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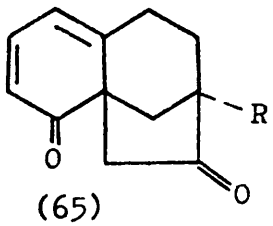

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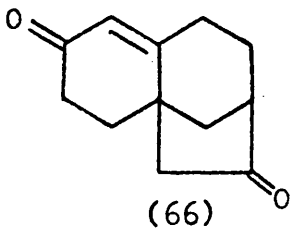
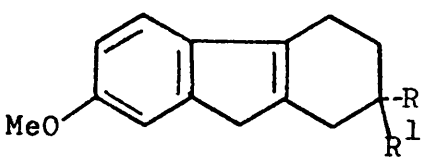


(66)

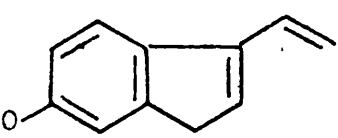
R=H, CF_3CO_2, CCl_3CO_2 in (61), (62), (64) and (65)



(67) R^1=$COCHN_2$, R^2=CF_3CO_2

(69) R^1=CO_2Et, R^2=OAc

(72) R^1=CO_2H, R^2=H



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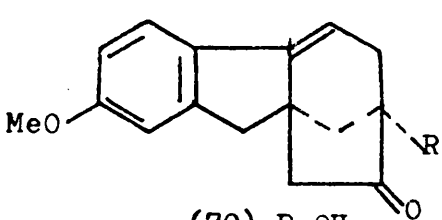
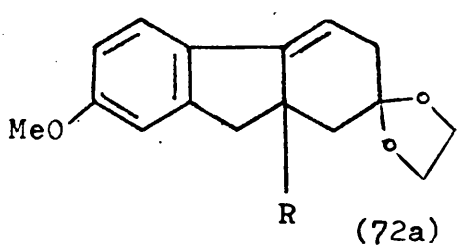


(70) R=OH

(71) R=H



(72a)

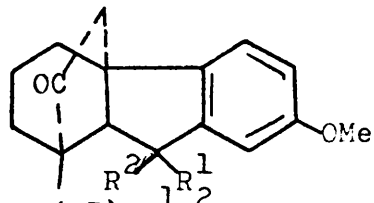
the diketone (57).

Mander approached the problem of synthesising the gibbane skeleton by preforming diazomethyl keto-hydrofluorenes[30]. The groundwork for this approach was carried out on the model compounds[31,32,33] (61), (62) and (63), prepared from the corresponding acids by successive treatment with oxalyl chloride and diazomethane. Treatment of the resulting diazo ketones afforded, in good yield, the tricyclic ketones (64), (65) and (66) respectively.

The precursor chosen for the gibbane synthesis was the diazo ketone (67), which has the added advantage in the presence of a potential 13-hydroxylated gibbane precursor. The diazo ketone was formed from the vinyl indene (68), obtained from 6-methoxyindanone, which underwent a Diels Alder cyclisation with ethyl α-acetoxyacrylate in boiling benzene to form the hydrofluorene (69). Base hydrolysis, protection of the resulting hydroxyl group as its trifluoroacetate, conversion of the acid to its acid chloride, followed by reaction with excess diazomethane, produced the diazo ketone (67). On stirring in trifluoroacetic acid, followed by base hydrolysis, almost quantitative yields of the tetracyclic ketone (70) were produced. Repeating the procedure with acrylonitrile as a dienophile produced excellent yields of ketone (71).

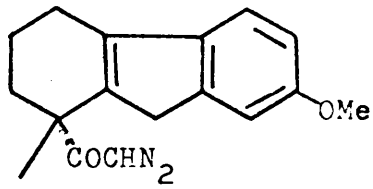
An independent approach to diazomethyl keto-hydrofluorenes was launched by Ghatak[34,35,36] who also prepared the olefin (71) starting from the reaction of 2,4-dicarboethoxycyclohexanone, m-methoxybenzyl chloride and sodium hydride, followed by saponification, decarboxylation and polyphosphoric acid promoted cyclisation to give moderate yields of hydrofluorene (72) which was cyclised to the keto-olefin (71) via its diazo ketone. However, Mander[30] has claimed that in his hands the reaction afforded a mixture of acid (72) and its 5-methoxy isomer.

Ghatak has also studied the stereochemistry of the hydrogenation of the cyclopropanes and olefins produced from such keto-carbenoid auditions, and, in general, the $\Delta^{9,11}$-gibbenes are hydrogenated to the unnatural configuration at C-9 unless a suitably orientated C-6 substituent is present, as discovered by Loewenthal[26,27]. The same criteria holds for



(73) $R^1R^2=O$

(76) $R^1=R^2=H$



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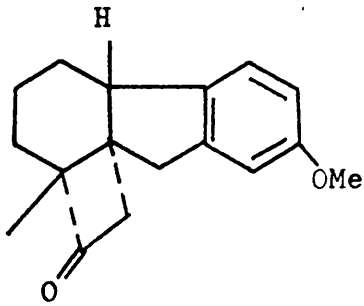
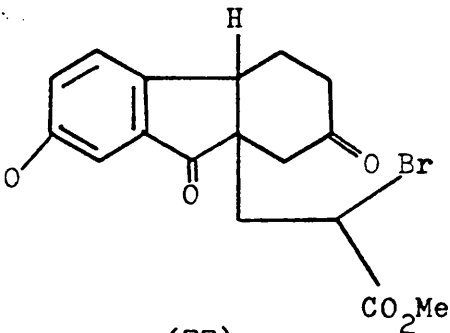


(75)



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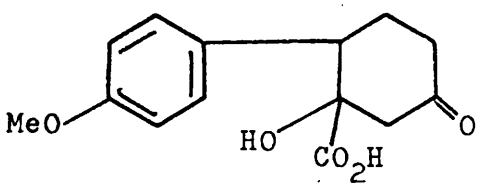

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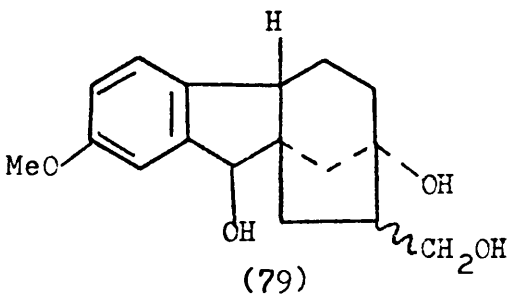

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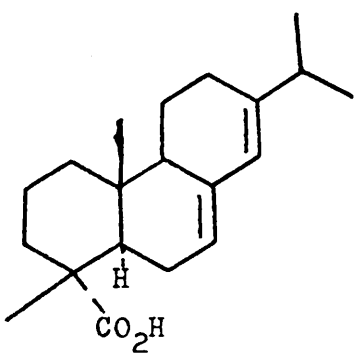

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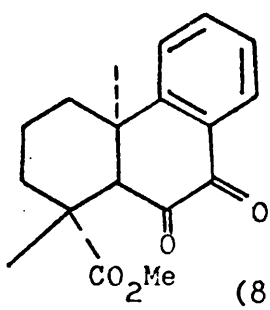

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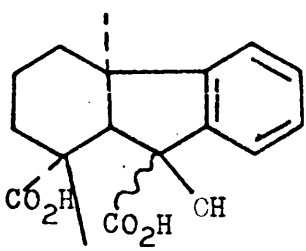


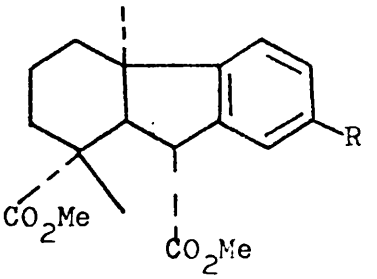
(82)

the hydrogenation of certain hydrofluorenes, which have been comprehensibly studied by Thompson[37]. Ketals of type (72a) were synthesised from 2-carboethoxy-4,4-ethylenedioxycyclohexanone, m-methoxybenzyl chloride and sodium hydride and then cyclised to give the 9a-carboethoxy derivative (72aR=CO_2Et). It was found that when R was CH_2OH or CO_2H then a 4aβ-hydrogen was produced on catalytic hydrogenation. however if R was CO_2alkyl then the natural 4aα-hydrogen resulted.

Utilising the high yield diazo ketone - olefin insertion reaction, Ghatak[38,39] synthesised the unusual hydrofluorene (73) from the accessible β,γ-unsaturated diazomethyl ketone (74). Photolysis of the diazo ketone (74) in the presence of cupric oxide produced after a stereocontrolled hydrogenation the cyclobutanone (75), treatment of which with a 24molar excess of triethyloxonium fluoroborate afforded the cyclopentanone (76) which underwent a benzylic oxidation with Jones reagent to afford the corresponding diazo ketone (73).

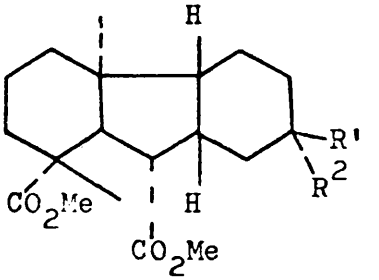
Ziegler[40] has used an efficient method for the preparation of the diketone (77) by condensing methyl vinyl ketone and p-methoxyphenylpyruvic acid to afford the acid (78) in high yield. Dehydration, catalytic hydrogenation and cyclodehydration with polyphosphoric acid afforded 7-methoxyhexahydrofluoren-9-dione. Selective ketalisation of the 2-oxo grouping followed by a Michael addition of methyl α-bromoacrylate and deketalisation produced the desired diketone (77), an internal Reformatzky reaction on which gave the polyfunctional gibb-A-triene (79).

A novel approach to the problem was recorded by the late Tahara[41] who synthesised gibberellin A12 (90) from what at first appears a most unusual source; l-abietic acid (80), but on a second glance it is not surprising, since ring contraction of the pimarane skeleton affords the hydrofluorene skeleton. Previous studies by the author[42] resulted in a hydrofluorene which was ideal as a basis for gibberellin A12 (90). Dehydration of l-abietic acid followed by chromic acid oxidation and esterification produced the diketo-ester (81), benzylic acid rearrangement of which produced the hydroxydiacid (82). Dehydration and hydrogenation of the acid produced,



(83) R=H

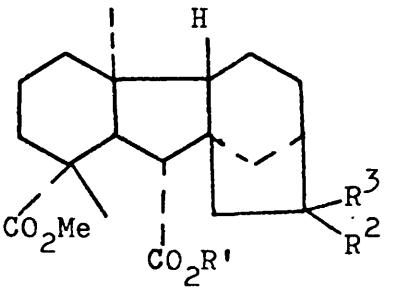
(84) R=OH



(85) R'=H, R^2=OH (86) R'R^2

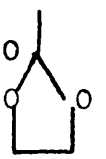
(87a) R'=H, R^2=CO_2H

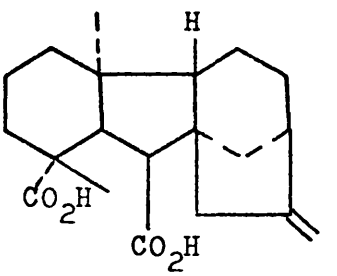
(87b) R'=CO_2H, R^2=H



(88) R'=Me, R^2R^3=O

(89) R'=H, R^2R^3=





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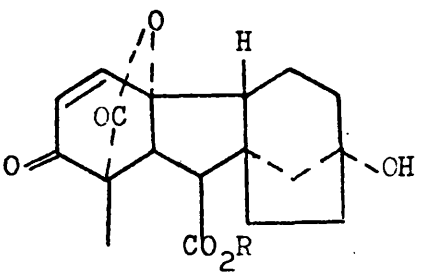
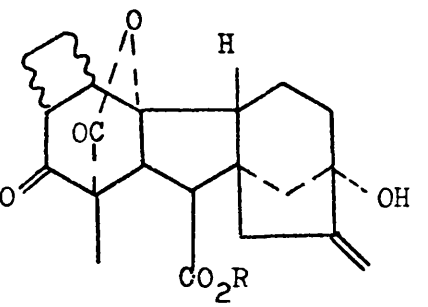


(91) R=H

(92) R=Me

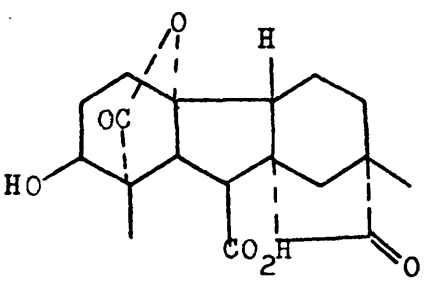


(93) a) 1α,2α,R=H

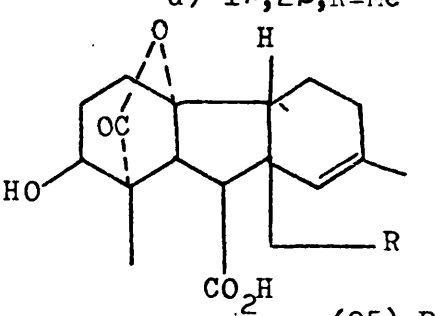
b) 1α,2α,R=Me

c) 1β,2β,R=H

d) 1β,2β,R=Me

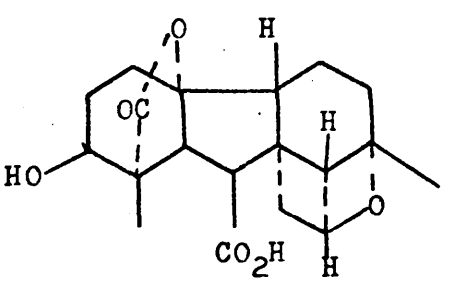


(94)



(95) R=CHO

(97) R=CH_2OH



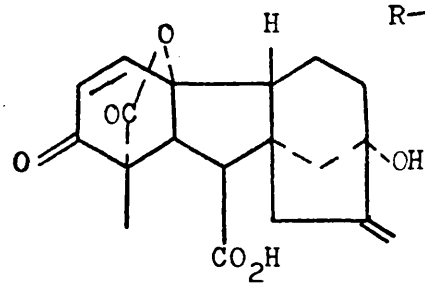
(96)

after esterification, the diester (83). Friedel Crafts acylation with acetyl chloride, Baeyer Villiger oxidation, hydrolysis with concentrated sulphuric acid gave the phenolic diester (84) regioselectively. Catalytic hydrogenation over ruthenium dioxide in ethanol at 100 atmospheres of pressure afforded the α-hydroxy diester (85). Jones oxidation, followed by a Wittig reaction with triphenylphosphonium iodide and sodium hydride, gave the 13-methylene diester (86). Hydroboration with diborane, followed by Jones oxidation, gave two seperable, isomeric acids (87a,b) from which the β-isomer (87b) was isolated and converted to its diazo ketone which underwent an intramolecular carbenoid insertion performed in benzene and copper sulphate while irradiated by a 300 watt tungsten lamp to afford the tetracyclic diester (88). Ketalisation and partial hydrolysis afforded the keto-ester (89). Deketalisation, followed by a Wittig reaction with triphenylmethylphosphonium iodide and sodium hydride gave pure gibberellin A12 (90) on demethylation.

b) Partial synthesis.

By far the most active group engaged in this field has been the German pairing of Lischewski and Adam, who, in the last few years, have studied both the chemical and photochemical partial synthesis of gibberellins and their synthons. Treatment of 10aα-hydroxy-3-oxo-4β-methylgibb-2-ene-4,6β-dicarboxylic acid-4,10-lactone (91) or its methyl ester (92) with ultra violet light in organic solvent e.g. methylene chloride, in the presence of ethene, gave the 1,2-ethylenegibbanes (93a,b,c,d). Treatment of (93c) with hydroxylamine in pyridine afforded the corresponding oxime, reduction of which with sodium boronydride gave the corresponding 1β,2β-ethylene-3β-hydroxy derivatives (110b), while direct reduction of (93a) with sodium borohydride afforded the corresponding 1α,2α-ethylene-3α-hydroxy derivative (110a).[43]

Gibberellin C (94) was then irradiated[44] and a Norrish 1 cleavage and consequent intramolecular (2+2) cycloaddition of the intermediate secoaldehyde (95) gave the



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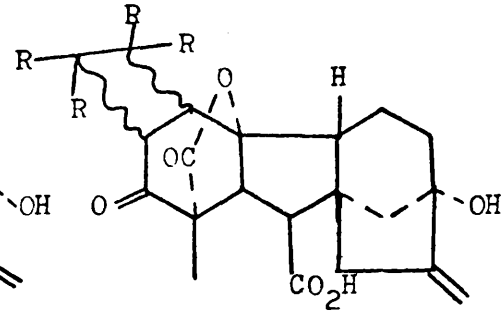
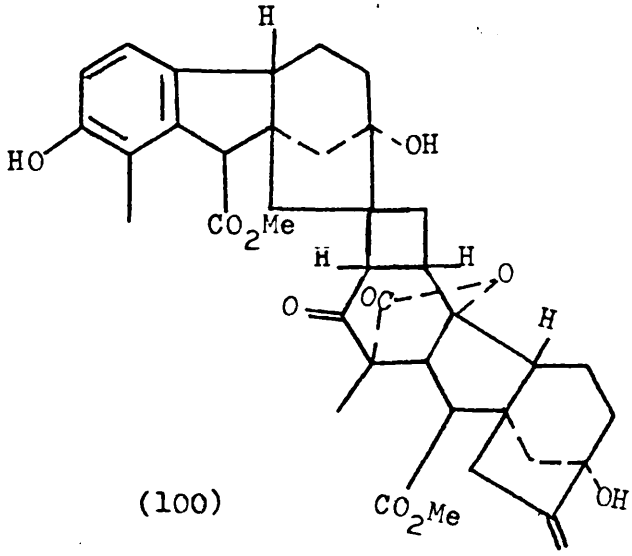
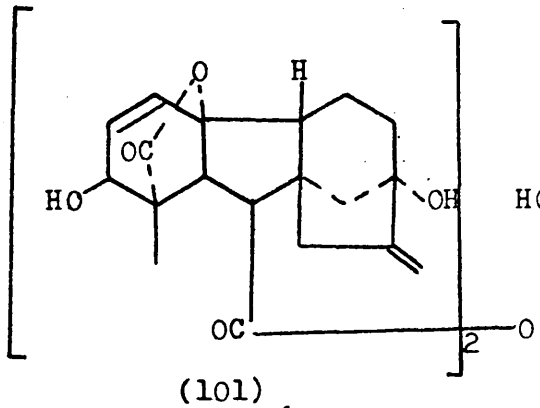


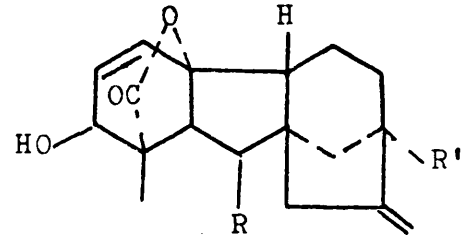
(99) a) 1α, 2α, R=H
b) 1β, 2β, R=H
c) 1α, 2α, R=Me
d) 1β, 2β, R=Me



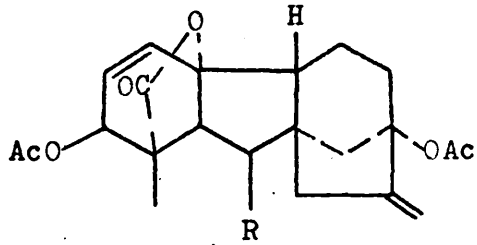
(100)



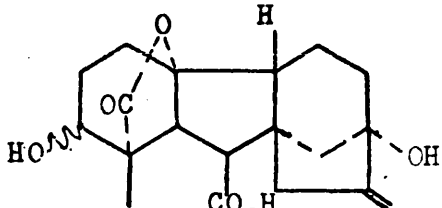
(101)



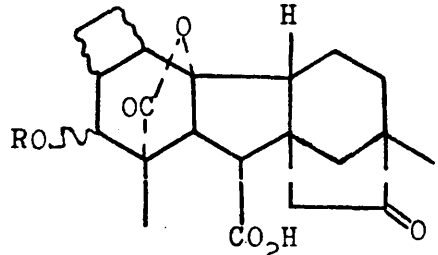
	R	R'
(102)	CHO	OH
(103)	CH_2OH	OH
(104)	CH_2OH	OH
(105)	CH_2I	OAc
(106)	CH_3	OH



(107) R=CH_2OH
(108) R=CHO



(110) a) 1α, 2α, αOH
b) 1β, 2β, βOH



(109) a) 1α, 2α, R=αOH
b) 1α, 2α, R=αOCOCF$_3$
c) 1β, 2β, R=βOH
d) 1β, 2β, R=βOCOCF$_3$

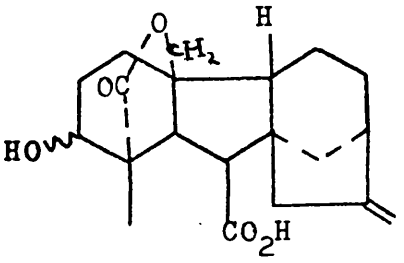
pentacyclic gibbane oxetane (96). The intermediate secoaldehyde could be isolated and reduced to the alcohol (97) by sodium borohydride treatment.

The work was continued[45] by investigating the photochemical (2+2) cycloaddition of ethene and tetramethylethene to 3-dehydrogibberellin A3 (98) under $n \rightarrow \pi^*$ excitation conditions. The reaction led to a 3:1 ratio of the cis-fused α- and β-cyclobutane annelated epimers (99a,b) as well as (99c,d) in 70 and 80% yield respectively. Sodium borohydride reduction of (99a) gave the 3α-hydroxy derivative stereospecifically whereas (99b) yielded the corresponding α- and β-hydroxy derivatives in a 1:6 ratio. This work had its basis in earlier studies[46] in which the 3-dehydrogibberellin A3 methyl ester was irradiated in the presence of ethene to give the aromatic ring A dimer (100).

Returning to the realms of chemical conversion, Adam[47] treated gibberellin A3 anhydride (101) successively with disodium ferrous carbonyl and dilute acid to produce gibberellin A3 aldehyde (102), which, on further reduction with sodium borohydride, afforded gibberellin A3 alcohol (103). This work was affiliated to the conversion of the said alcohol into 6β-methyl-norgibberellin A3[48] (106) by the specific conversion of the alcohol (103) to its diacetate (104), followed by the transformation of the primary alcohol to its primary alkyl iodide (105), reductive removal of the halide by triethyltin hydride, and finally removal of the protecting acetyl function with sodium methoxide to produce the β-methyl gibberellin (106).

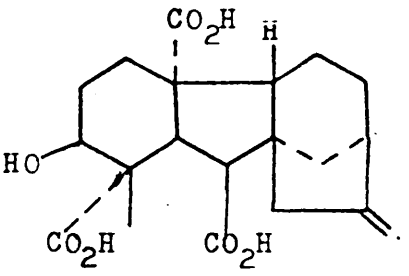
The reduction of the diacetate (107) to gibberellin A3 aldehyde was also studied[49]. Treatment of the primary alcohol with Corey's[50] dimethyl sulphide/N-chlorosuccinimide complex in the presence of triethylamine, produced the corresponding diacetoxy aldehyde (108), which, on removal of the protecting acetoxy units, afforded the desired aldehyde (102).

Recently[51] these prodigious researchers studied the structure and molecular packing of the cyclobutane annelated pseudogibberellin A1 derivatives (109a,b,c,d) prepared by trifluoroacetic acid catalysed Wagner-Meerwein rearrangement of diols (110a,b).



(111) a) α-OH

b) β-OH



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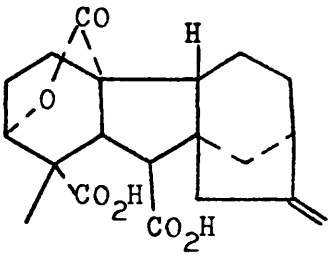
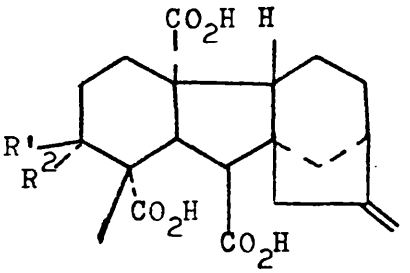


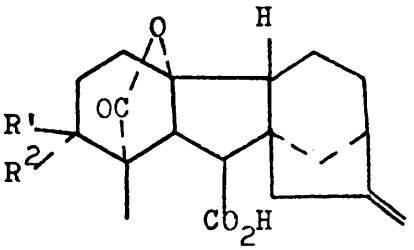
(113)



(114)

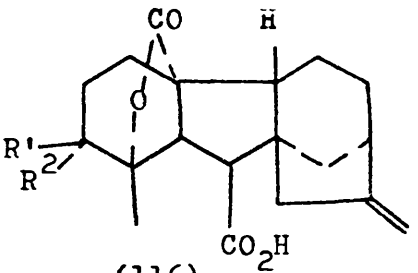
R'	R^2
OH	H
H	H
OAc	H

O



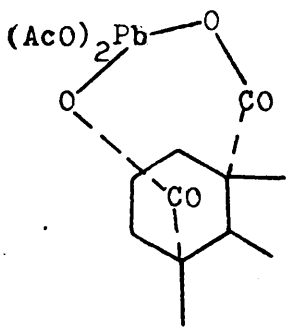
(115)

R' and R^2 as for (114)



(116)

R' and R^2 as for (114)



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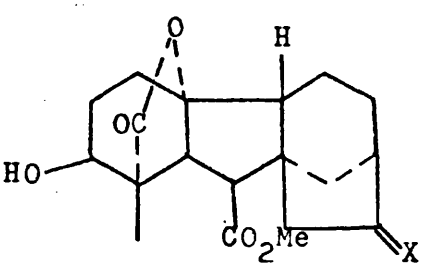
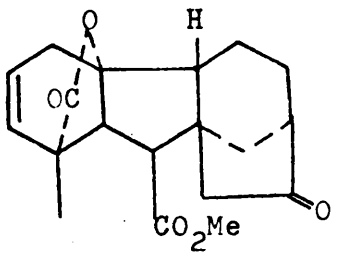
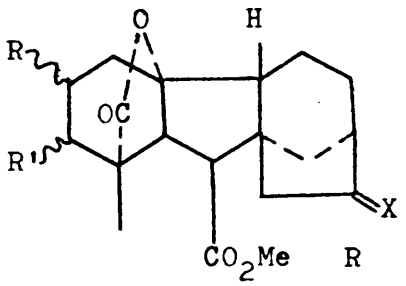


(118) X=O

(119) X=CH_2

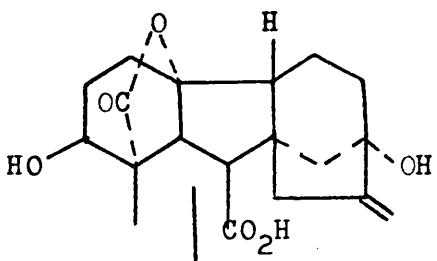


(120)

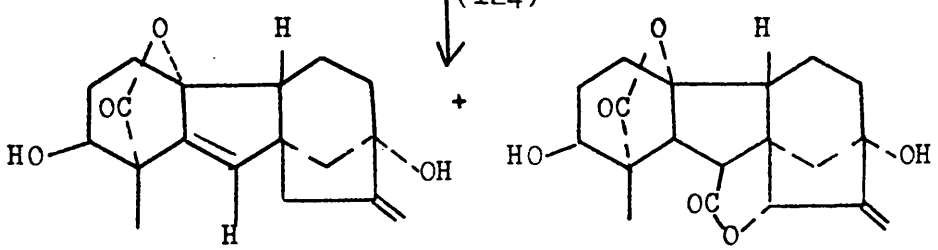


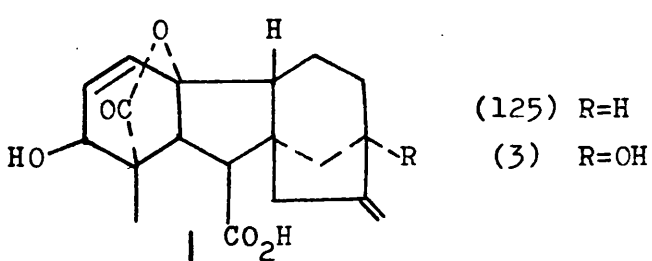
	R	R'	X
(121)	α OAc	β Br	O
(122)	α OAc	H	CH_2
(123)	α OH	H	CH_2

SCHEME 1



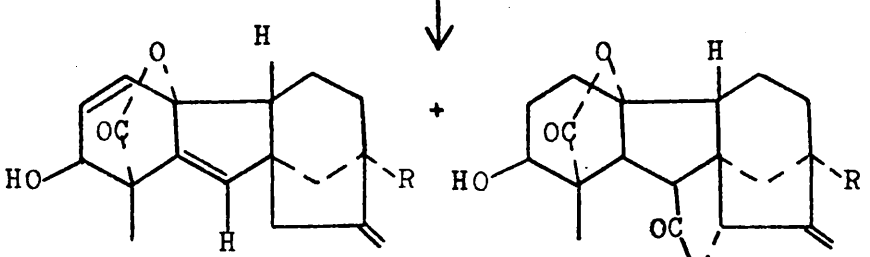
(124)





(125) R=H

(3) R=OH

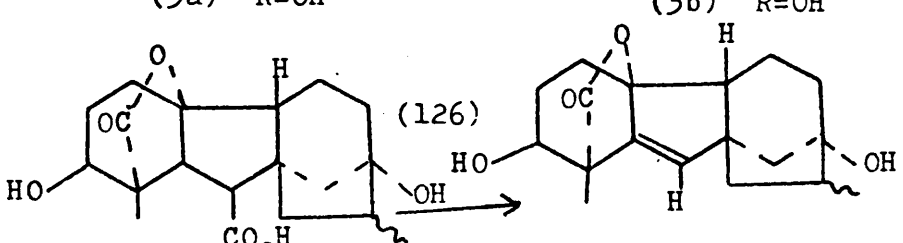


(125a) R=H

(3a) R=OH

(125b) R=H

(3b) R=OH

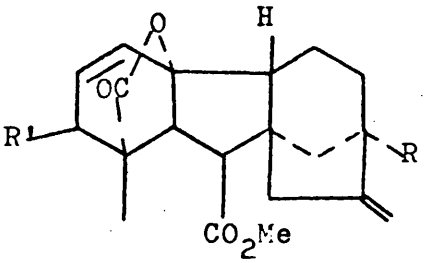


Another group of workers challenging Adam's supremacy is that headed by MacMillan; a name revered in gibberellin biosynthetic studies. He achieved the synthesis of gibberellin A37[52,53] (111b) via the selective reduction of the hindered 10-carboxy group in gibberellin A13 (112) based on earlier work by Cross[54], in which gibberellin A13 was converted into some δ-lactones related to gibberellin A15. The route chosen involved Jones oxidation of gibberellin A13 followed by sodium borohydride reduction and thermolytic lactonisation of the resultant mixture to afford the 20,3-lactone (113), reduction of which, with lithium borohydride, gave directly, the corresponding 19,20-lactone (111a). Epimerisation to the required β-epimer (111b) was effected by Jones oxidation followed by Meerwein-Ponndorf reduction.

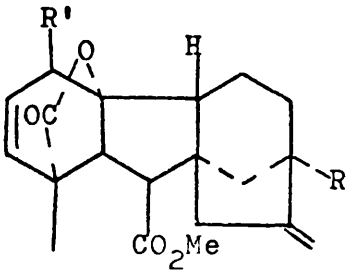
This work was quickly followed by the first chemical correlation between C_{20} and C_{19} gibberellins[55] by the oxidative decarboxylation of ent-gibberellane-19,20-dioic acids (114) with lead tetraacetate to yield mixtures of 19,10- and 20,4-lactones (116) via the intermediate (117).

Concurrent research into the characterisation of gibberellins A46 and A47 disclosed the partial synthesis of 2-hydroxygibberellins from their 3-hydroxy isomers[56] as illustrated by the treatment of the known nor-ketone obtained by oxidation with osmium tetroxide and periodate of gibberellin A4 methyl ester (119), with phosphoryl chloride, resulting in the formation of the olefin (120). Reaction of the olefin with N-bromoacetamide and lithium acetate gave the bromoacetate (121), reduction of which, both regio- and stereospecifically, with tri-n-butyltin hydride, followed by methylenetriphenylphosphorane treatment, afforded the acetate (122). Hydrolysis of the acetate gave the 2-hydroxy isomer of gibberellin A4 methyl ester (123).

Recently, two Russians[57] have investigated the oxidative lactonisation and oxidative decarboxylation of gibberellins A3 (3), A1 (124) and A7 (125) with neutral manganese dioxide and found that the presence of a Δ^{16} double bond was essential for the occurrence of oxidative lactonisation at C-15, as illustrated by the reaction of tetrahydrogibberellic acid (126) under similar conditions, when no lactonisation



(127) R=OH, R'=F



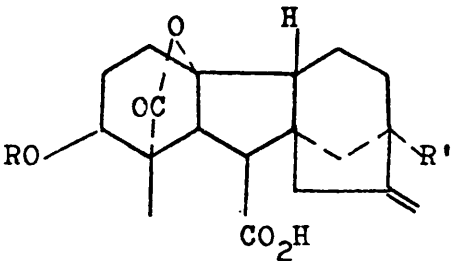
(128) R=OH, R'=F

(129) R=F, R'=F

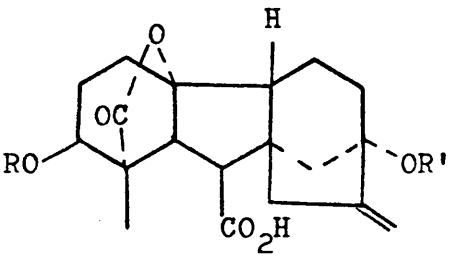
(130) R=F, R'=F

(131) R=F, R'=H

(132) R=F, R'=H



(133) R=X, R'=OH



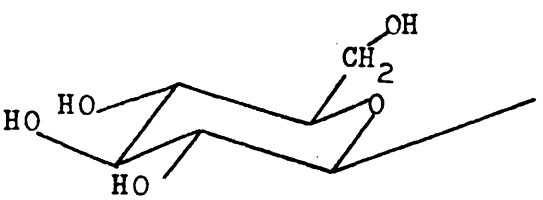
(134) R=X, R'=H

(135) R=X, R'=H

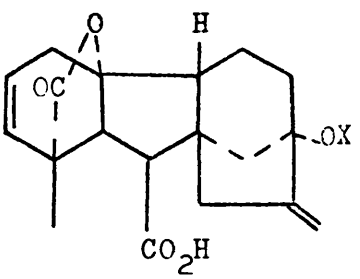
(137) R=H, R'=X

(136) R=H, R'=OX

(139) R=X, R'=X



(X)



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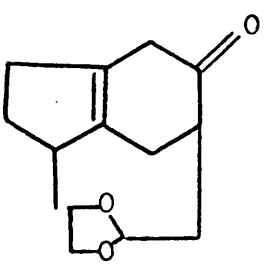

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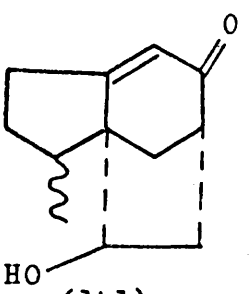


(141)

occurred (scheme 1). This work was an improvement on the earlier observation[58] that gibberellic acid (3) afforded, under similar conditions, the products (3a) and (3b) in poor yields.

A rather interesting study concerning the biological activities of fluorogibberellins[59,60] has recently inspired their synthesis. Until 1974, the major route involved the microbiological production of fluorogibberellic acid by mould metabolites[61], however Cross has now been able to partially synthesise fluorogibberellins much more economically[62,63] by the reaction between hydroxy-gibberellins and 2-chloro-N,N-diethyl-1,1,2-trifluoroethylamine, with the allylic 3β-hydroxyl group of gibberellic acid methyl ester being converted to the corresponding ester of 3β-fluorogibberellins (127) and their allylic isomers (128). This method was an improvement over his earlier fluorinating agent, which consisted of an adduct between caesium fluoride and N,N-dimethylacetamide[64]. The reaction was modified to achieve the difluorinated gibberellins (129) and (130). Selective reductive removal of the secondary halide by tri-n-butyltin hydride afforded the monofluoride derivatives (131) and (132).

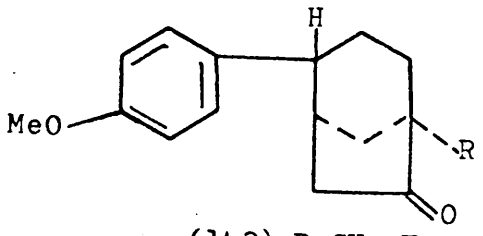
Schneider[65,66] has successfully synthesised O(3)-β-D-glucopyranosides of gibberellins A1 (133), A3 (134) and A4 (135) as well as the O(13)-β-D-glucopyranosides of gibberellins A1 (136), A3 (137) and A5 (138) by means of the Koenigs-Knorr reaction. In addition to their monoglucosides, the gibberellin A3-O(3,13)-di-β-D-glucopyranoside (139) has been synthesised.

c) Construction of gibberellins and their synthons via the formation of bicyclo(3.2.1)octanes.

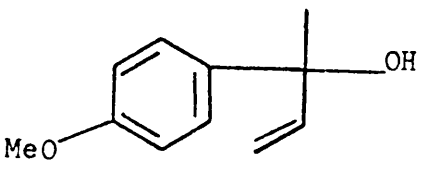
1) Acid catalysed cyclisations.

By a novel procedure, Wiesner[67] cyclised the unsaturated keto-acetal (140) by heating in 80% acetic acid to give a mixture of tricyclic epimers (141) in excellent yield.

An interesting approach, which involves the in



(142) R=CH_3,H



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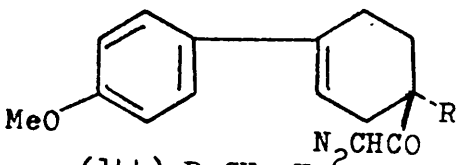
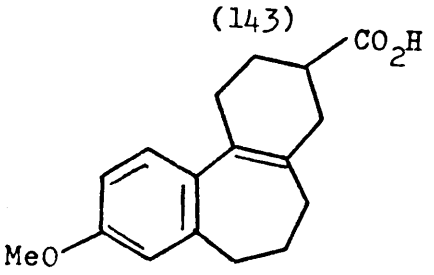


(144) R=CH_3,H



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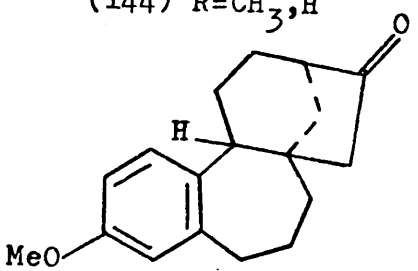

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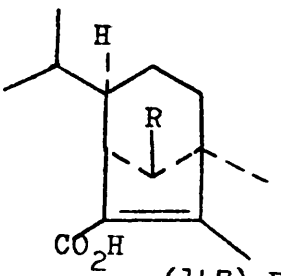
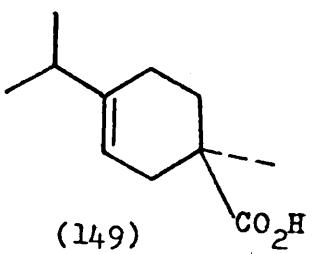


(147) R=CH_2OH

(148) R=H



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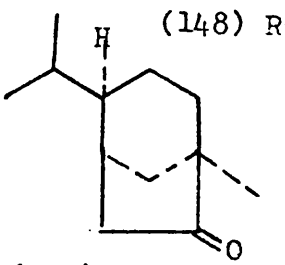

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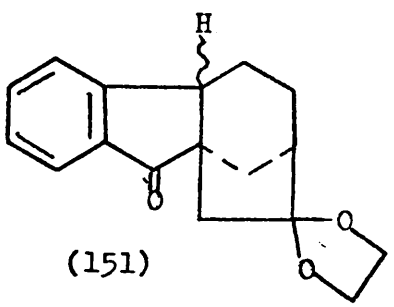

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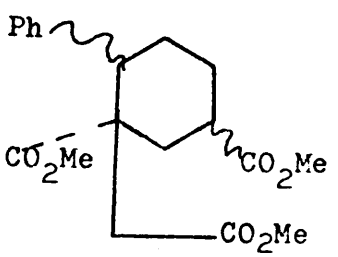

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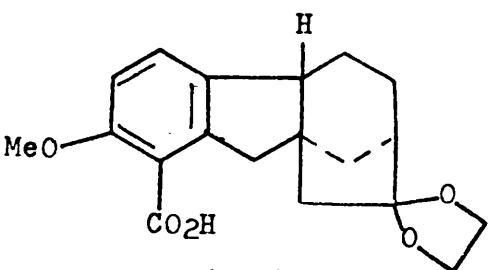

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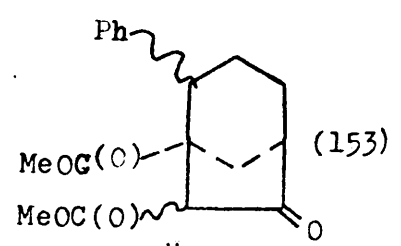

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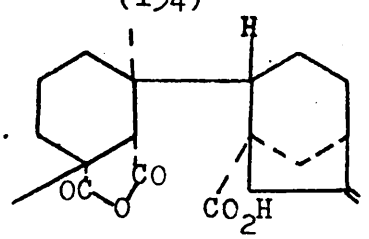

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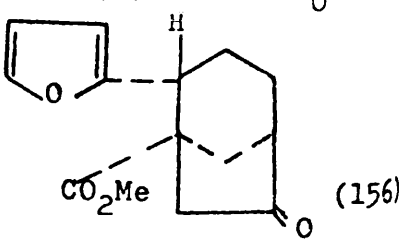


(156)

vogue reaction of the cyclisation of unsaturated diazo ketones, has been rigorously studied by two independent groups headed by Ghatak and Mander. Ghatak[68] has synthesised the endo-2-aryl-6-oxobicyclo(3.2.1)octane derivatives (142) by the Diels Alder cyclisation of the carbinol (143) and either methyl acrylate (144:R=H) or methyl methacrylate (144:R=Me), followed by saponification and conversion of the resulting acid to its diazomethyl ketone (144) by standard procedures. Boron trifluoride etherate catalysed cyclisation afforded the bicyclo(3.2.1)octanones (142) in high yields.

Lately[69,70], he has been investigating the cyclisation of tricyclics to tetracyclics by a similar procedure, as exemplified by the conversion of the tricyclic acid (145) to the tetracyclic ketone (146) in 50% yield. Other examples are included in the hydrofluorene section.

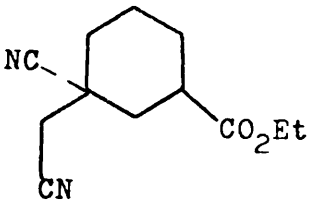
Mander, who also favours the hydrofluorene approach, has published two papers on the synthesis of the 14-norhelminthosporic acid analogue (148), which shows gibberellin-like properties[71,72]. The key step in a multistage synthesis involved the cyclisation of the acid (149), via its diazo ketone, to the ketone (150) using boron trifluoride etherate in nitromethane (Helminthsporic acid = (147)).

2) Base catalysed cyclisations.

In her synthesis of the gibbane (151) Gerber[73] used a Dieckmann cyclisation to construct the CD ring system (153) from (152). This approach was taken up by Baker[17,29] in his synthesis of the advanced gibberellin synthon (154).

Recently, Kato[74,75] utilised this technique in his synthetic approach to the gibberellin-like synthon fujenoic acid (155). Diels Alder reaction between methyl furfurydenecrotonate and methyl itaconate, followed by sequential catalytic hydrogenation, Dieckmann cyclisation and decarbomethoxylation produced the keto-ester (156).

A similar approach was adopted by a quartet of Frenchmen[76] who synthesised the bicyclooctanone (157) from 3-carboethoxycyclohexanone, which, on Knoevenagal condensation conditions in the presence of ethyl cyanoacetate, followed



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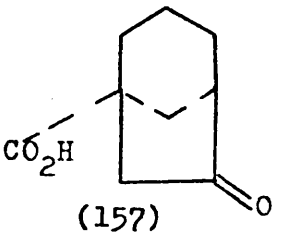

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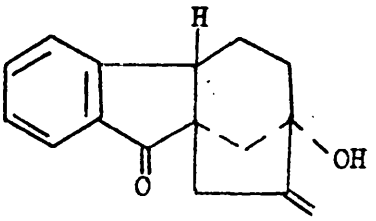

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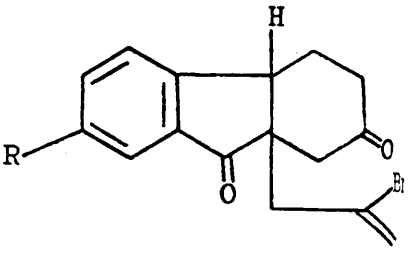
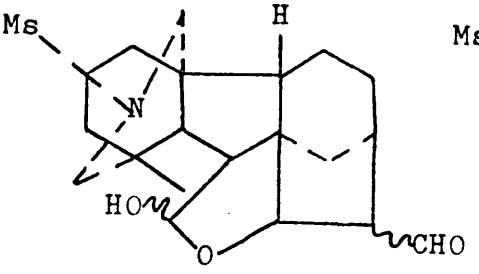


(160) R=H

(161) R=OMe



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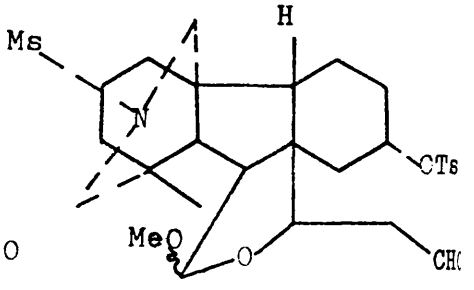

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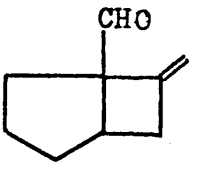

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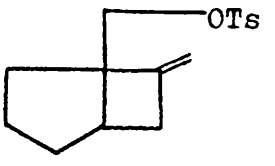

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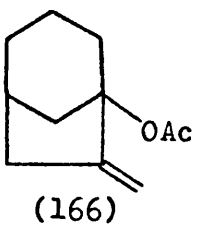

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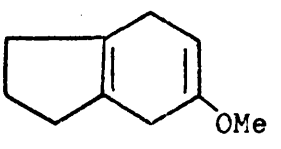

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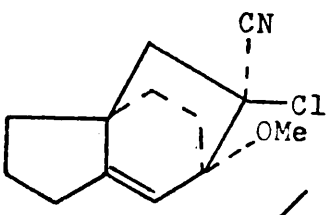

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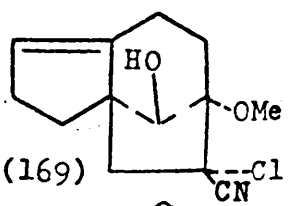

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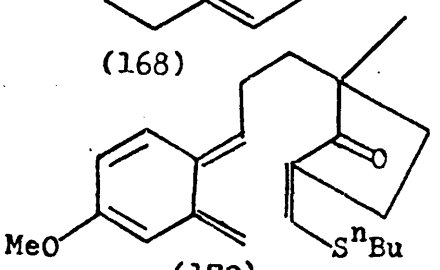

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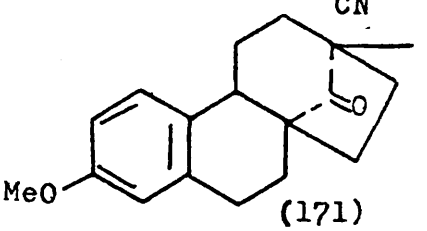


(171)

by treatment with potassium cyanide, afforded the ester (158) in 60% yield. This compound then underwent a Dieckmann-like cyclisation followed by basic hydrolysis and decarboxylation to yield the acid (157) in 65% yield.

The hydroxy-ketone (159) was prepared by Corey.[77] from the bromo-diketone (160) using di-n-butylcopper lithium in ether at -50°. A similar cyclisation of the bromo-diketone (161), via an intramolecular Grignard reaction carried out by Ziegler[78] was unsuccessful due to internal protonation, presumably from enolisation of the aliphatic carbonyl.

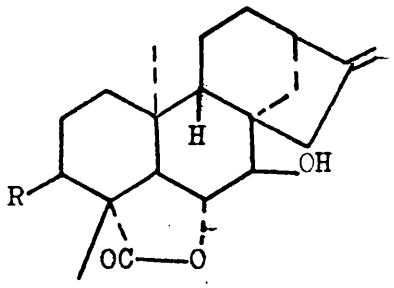
In his total synthesis of gibberellin A15, Nagata[79] effected the ring D closure of the complex synthon (162) to the bicyclooctane derivative (163) using pyrrolidine in methanol/N-methylpyrrolidine, followed by acid hydrolysis.

3) Pericyclic reactions.

Ziegler[80] produced from the photoaddition between allene and 1-cyclopenten-1-carboxaldehyde in ether, the photoadduct (164) in 69% yield. Reduction of the aldehyde followed by tosylation of the resulting alcohol afforded the tosylate (165) in 80% yield. Solvolysis in 10% sodium acetate/ acetic acid at 118° gave the acetate (166).

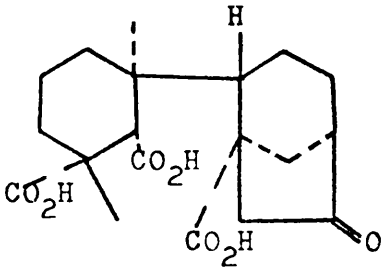
Yamada[81] produced a more promising entity by the Diels Alder reaction of the dihydroindane (167) with 2-chloroacrylonitrile at 120° to afford the olefin (168), isolable from an epimeric mixture. Treatment with m-chloroperbenzoic acid afforded the corresponding α-epoxide exclusively which underwent a skeletal rearrangement to produce the polyfunctional tetracyclic (169). This provides an attractive alternative to his earlier work in which rings ABC were constructed from a suitable aromatic precursor serving as a protected ring C equivalent[21,22].

Kametani[82,83,84] synthesised a more attractive potential intermediate for tetracyclic diterpenoids by an intramolecular cycloaddition of the o-quinodimethane (170) which, on desulphurisation, afforded the ethano-octahydromethoxyphenanthrenone (171).



(172) R=H

(176) R=OH



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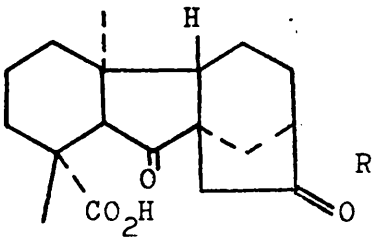
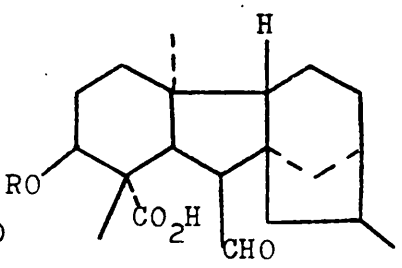
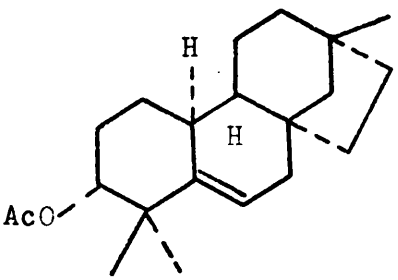


(174)



(175) R=H

(177) R=THP



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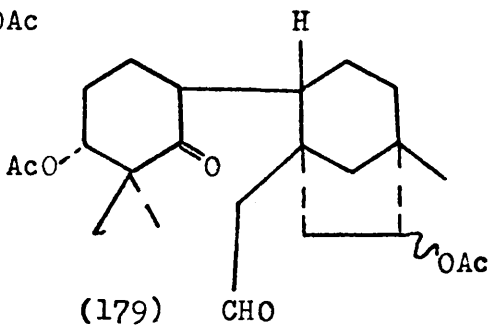

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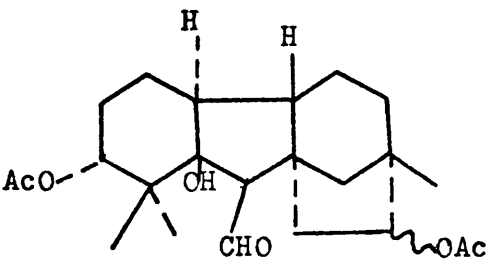

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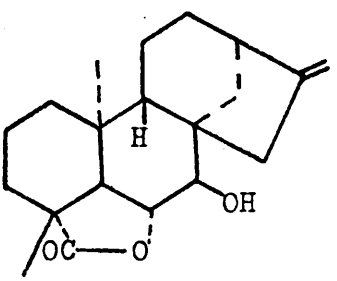

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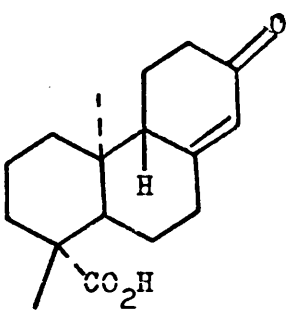


(182)

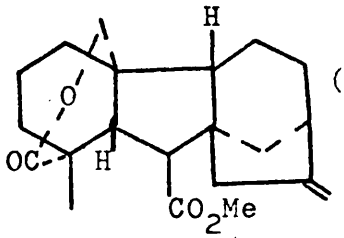
4) Ring contraction of kauranes.

In a series of papers investigating routes to the gibberellins, Galt and Hanson[85] converted the 7-hydroxy-kaurenolide (172) to the dicarboxylic acid (173) in three steps. Treatment with refluxing acetic anhydride produced the internal 6,7-anhydride which, on pyrolysis at 280°, gave the diketone (174).

Utilising this procedure, MacMillan[86] was able to prepare gibberellin A14 aldehyde (175) from the 3β,7β-dihydroxykaurenolide (176). He later improved upon this sequence by mimicking the method employed by Cross[87] by selectively protecting the 3-hydroxyl group of the alcohol (176) as its tetrahydropyranyl ether, epimerising the 7β-hydroxyl group to its 7α-analogue, followed by the formation of its 7α-p-toluenesulphonate, which on treatment with potassium hydroxide in t-butanol, afforded the 3β-tetrahydropyranyl ether (177) in excellent yield.

By far the most prolific group engaged in the synthesis of gibberellins has been that headed by the Japanese pairing of Mori and Matsui, who in an almost uninterupted series of publications since Yabuta first isolated a crystalline gibberellin[2] , have synthesised a wide variety of hydrofluorene derivatives. As an alternative mode of approach, Mori[88] employed a sequence involving the ring contraction of the kaurene (178) by ozonolysis and a reductive work up, which resulted in the formation of a keto-aldehyde (179) which underwent an intramolecular aldol condensation when chromatographed on alumina to give the gibbane (180). This work was followed by his total synthesis of gibberellin A12[89] (90) in which he employed methyl-7,16-dioxo-17-norkauran-19-oate as a relay compound. He then synthesised the lactone (181), which underwent a ring contraction to afford gibberellin A12 (90). Since this lactone could be synthesised from ethyl-1-methylcyclohexan-2-one-1-carboxylate[90] via methyl-7-oxopodocarp-8-en-16-oate (182) in about three dozen steps it completed the formal total synthesis.

A rival group of Japanese investigators, headed by Fujita, adopted a similar strategy in their synthesis of



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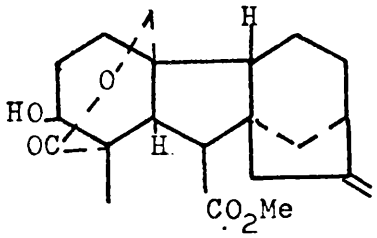

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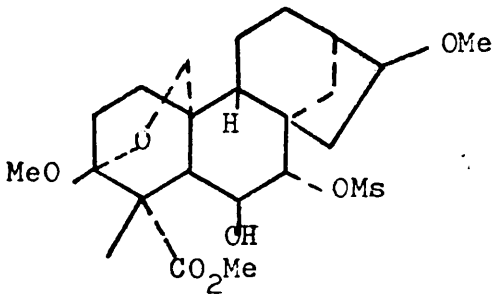
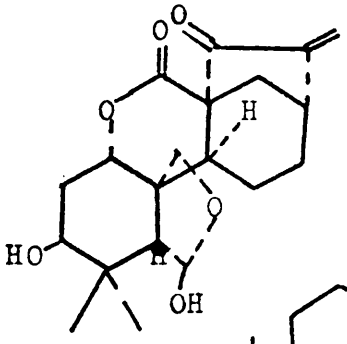


(185)



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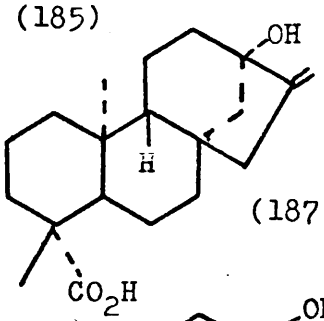

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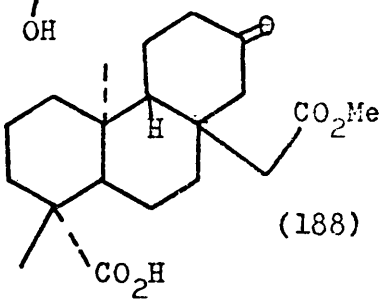

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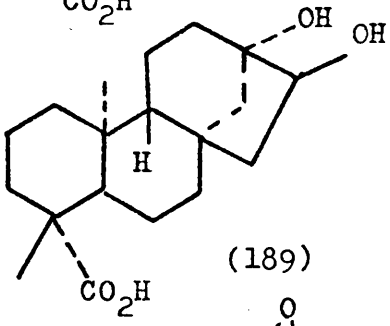

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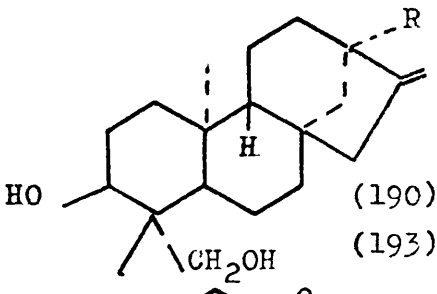
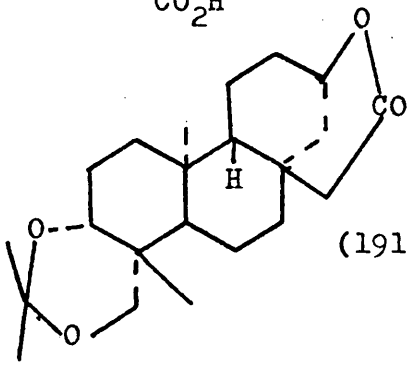
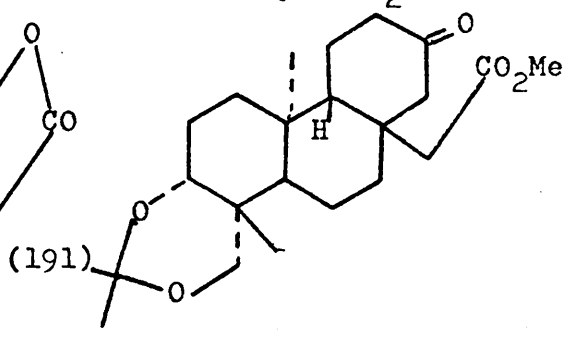


(190) R=H

(193) R=OH





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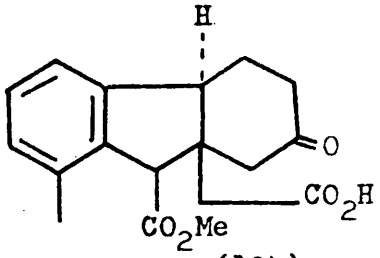
(192)



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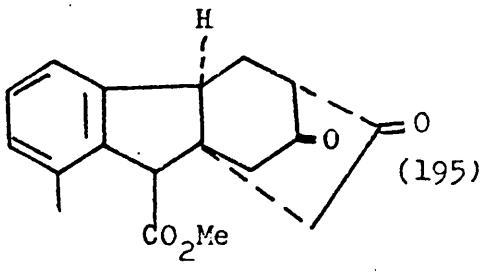

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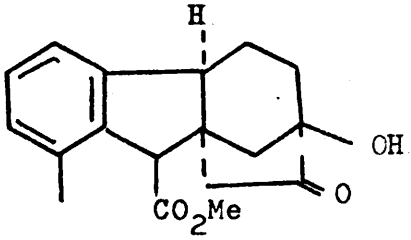


(196)

gibberellin A15 methyl ester (183) and gibberellin A37 methyl ester[91,92] (184) derived from the kaurane-like intermediate (185), which, on treatment with methanolic sodium methoxide, afforded the gibbane skeleton. Since enmein (186) was a key intermediate, the prior synthesis of which had been accomplished[93] from 1,6-dihydroxynaphthalene by innumerable steps, then this represented a total synthesis of gibberellins.

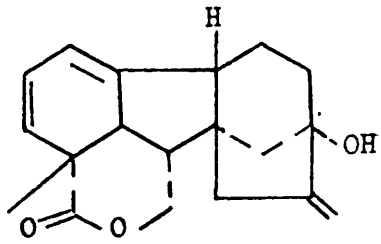
Fujita[94] has intensively studied the conversion of the kaurane skeleton to that of a gibberellin and has confirmed the earlier work of MacMillan[86] which proposed that a prerequisite for a smooth ring B contraction was an antiperiplanar stereochemistry between the migrating bond and the leaving group i.e. C-5—C-6 and C-7—O bonds must be antiperiplanar.

5) Radical anion cyclisations.

Cook[95] has used an acyloin condensation to construct the bicyclo(3.2.1)octane system in his synthesis of steviol (187). Keto-ester (188) was converted to the diol (189) using a liquid ammonia, sodium, tetrahydrofuran reduction medium. He later modified this reaction[96] in such a manner that an α-hydroxyl group could be introduced into a 7-methylenebicyclo(3.2.1)octane system. Thus, treatment of the natural endiol (190) by a Lemieux-Johnson oxidation, followed by a Baeyer-Villiger oxidation and subsequent protection of the diol by ketalisation resulted in the ketal (191). Acid hydrolysis, followed by esterification, afforded the keto-ester (192), which, on treatment with sodium in naphthalene, afforded, after a Wittig reaction and acid catalysed diol reformation, the required triol (193).

A method of transforming a trans-fused BC ring system into a cis-fused BCD ring system was demonstrated by Mori[97]. The keto-acid (194) was readily converted into the bicyclo(2.2.2)octane derivative (195) which, on subjection to pinacol reduction conditions, yielded the cis-fused BC ring gibbane (196).

The pinacol type cyclisation has also been



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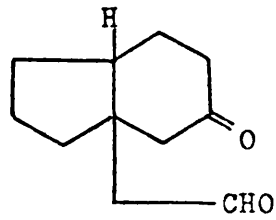

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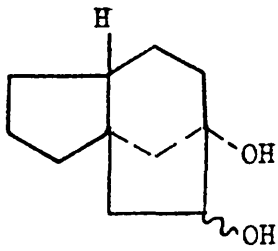

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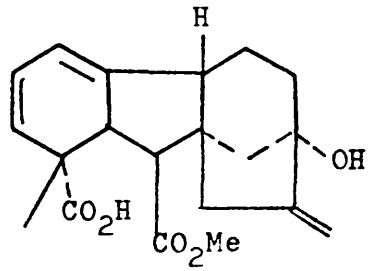

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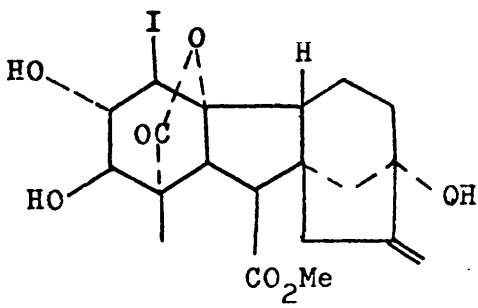

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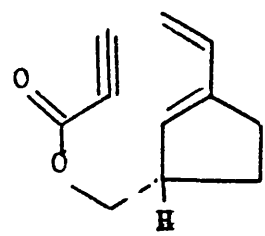

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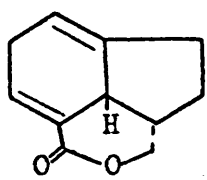

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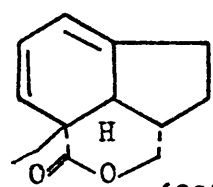

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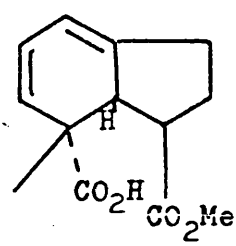


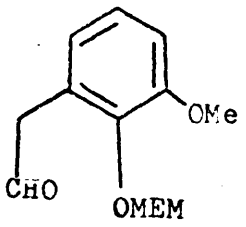
(205)

studied by Corey and is a key step in his synthesis of the gibberellic acid precursor[98] (197). Earlier studies on model compounds were encouraging, with the keto-aldehyde (198) forming the diol (199) on treatment with magnesium amalgam and dimethyldichlorosilane in tetrahydrofuran, with the yield of crude diol being 75%[99]. This reaction was improved upon by reduction with the complex formed on addition of six equivalents of cyclopentadienyltitanium trichloride to four and one half equivalents of lithium aluminium hydride at 50° in tetrahydrofuran, followed by the rapid addition of the keto-aldehyde. This resulted in a 90% yield of isolated diol. This was the final study on model compounds prior to the embarkation onto a synthetic route to gibberellic acid (3).

Previous work on the triene-acid[100] (200), readily available from gibberellic acid (3) by successive treatment with p-toluenesulphonyl chloride and sodium bromide followed by elimination of hydrogen bromide, established that it could be readily reconverted to gibberellic acid by the regioselective oxidation with m-chloroperbenzoic acid to afford, after saponification and iodine treatment, the lactone (201). Conversion of the lactone (201) to the desired product was achieved by trifluoroacetylation, elimination with zinc dust and detrifluoroacetylation with aqueous sodium bicarbonate.

Model studies on the formation of rings A and B of the triene (200) were also successfully completed[101]. The key step involved the intramolecular Diels Alder cyclisation of the readily prepared diene-ester (202), from 2,5-diethyl-1-cyclopentanonedicarboxylate to form the lactone (203), which was alkylated to afford the corresponding diene-lactone (204). Hydrolysis and oxidation gave the required diene-acid (205) after a selective methylation via an iodolactone intermediate.

Thus model studies had fully functionalised rings A and B into one segment of the target molecule (200) and rings C and D into another. Since rings C and D had less functionality and required more forcing conditions than the formation of the AB ring junction, then their synthesis received priority. Claisen rearrangement of guaiacol allyl



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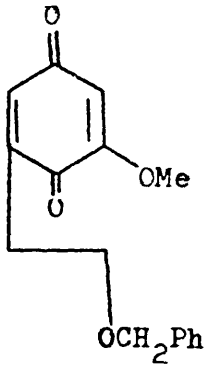

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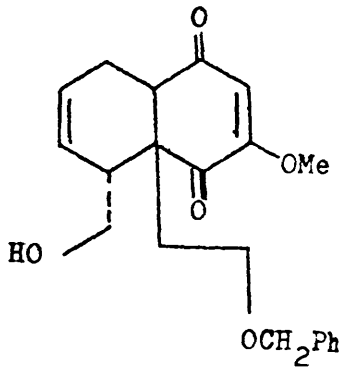
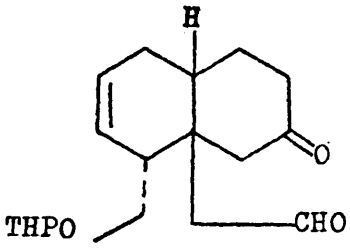


(208)

MEM= $CH_3OCH_2CH_2OCH_2$-



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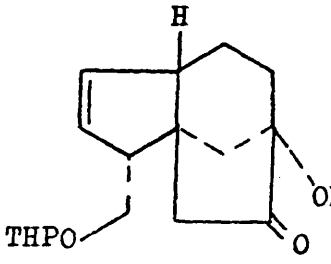

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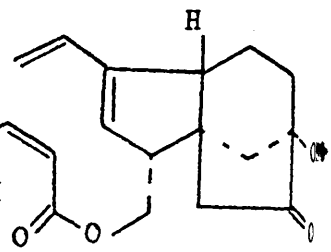

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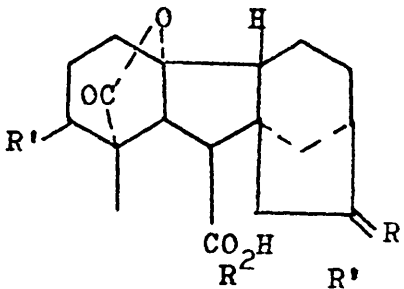
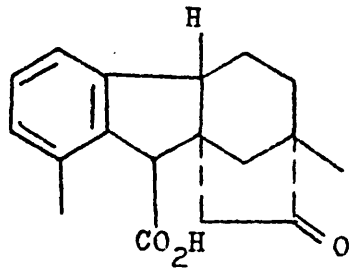


	R²	R'
(212)	Me, OH	OH
(213)	CH_2	OH
(214)	CH_2	H
(215)	Me, OH	H



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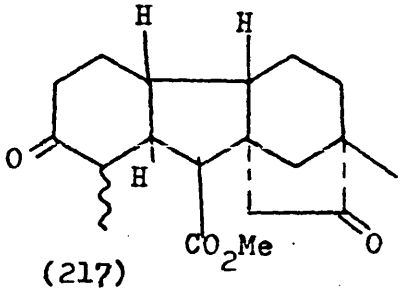
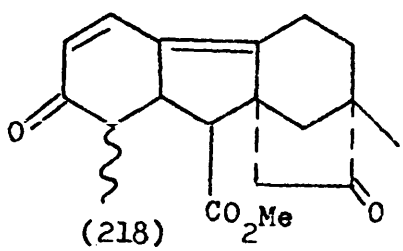


(217)



(218)

ether, followed by β-methoxyethoxymethyl ether formation and Lemieux-Johnson oxidation afforded the aldehyde (206) which was converted to the quinone (207) in four steps. Diels Alder reaction with penta-2,4-dienol afforded the adduct (208) stereospecifically, which was converted to the keto-aldehyde (209) in seven steps. Pinacol cyclisation, oxidation of the resulting secondary alcohol to the corresponding ketone, β-methoxyethoxymethyl ether protection of the newly formed tertiary alcohol, Lemieux-Johnson oxidation and an intramolecular aldol condensation formed the tricyclic keto-aldehyde (210). Wittig reaction, removal of the tetrahydropyranyl ether protecting the primary alcohol group which has to orientate the forthcoming dienophile, and reaction with β-chloroacrylyl chloride supplied the triene (211). Diels Alder cyclisation in benzene, α-lactone methylation, elimination of hydrogen chloride and removal of the β-hydroxyl protecting group afforded the target molecule (197). Unfortunately, to date, this molecule has refused to undergo an oxidative hydrolysis, thus preventing the formation of his original goal (200), despite the ease of hydrolysis of the model compound (204). With his usual prowess, Corey succeded in performing every reaction sequence in greater than 85% yield of isolated product.

A review of gibberellin synthesis would be incomplete without mentioning the mammoth undertaking of the total synthesis of gibberellins A2 (212), A4 (213), A9 (214) and A10 (215) from o-xylene, by the Japanese group headed by Mori[102].

The route involved five separate stages and was achieved by correlation with a variety of degradation products of gibberellic acid (3) which were then used as relay compounds, since their synthesis involved a multitude of steps, the majority of which were low yielding.

The first stage in the total synthesis involved the conversion of o-xylene to epigibberic acid (216) in a 21 stage sequence[103]. This was then elaborated to the diketo-ester (217) in a 5 step procedure, followed by separation of the epimeric product. This ester was shown to be identical with a new degradation product of gibberellic acid and served as another relay compound. Transformation of

the diketo-ester (217) into the dienone (218) was achieved in 10 steps.

Previously, Mori[104] had successfully performed the partial synthesis of gibberellin C (94) from the dienone (218), and since Cross[105] had partially synthesised gibberellin A4 (213) from gibberellin C, then this constituted a total synthesis of gibberellin A4. Also, gibberellins A2[106], A9[107] and A10[108] had been partially synthesised from gibberellin A4, so these three gibberellins were also totally synthesised.

Although the total synthesis of gibberellins C, A2, A4 , A9 and A10 reported by Mori are meritorious, they are of little practical value because of their numerous steps.

This thesis is concerned with the development of an efficient and stereospecific route to suitably substituted hydrofluorenes which can be further elaborated to gibberellin A4 precursors.

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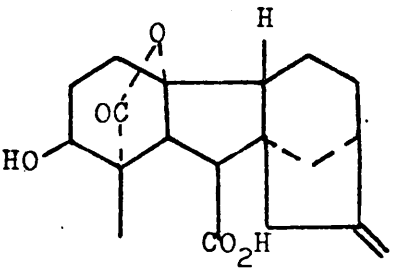

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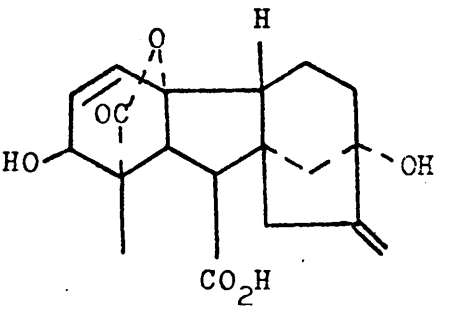

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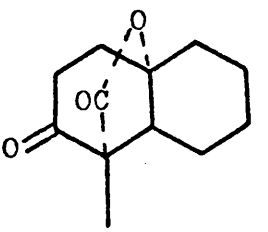

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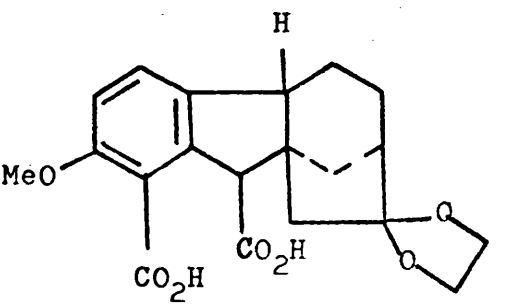


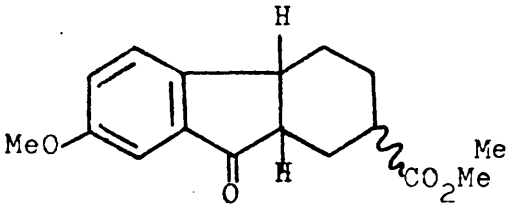
(4)

DISCUSSION.

The total synthesis of gibberellin A4 (1) has intrigued chemists ever since Scott and Sim[1] provided inexpugnable proof concerning the structure and absolute stereochemistry of gibberellic acid (2). Although gibberellin A4 possesses four different functional groups it contains a complex carbon framework incorporating eight chiral centres which has succumbed the synthetic plans of even the most illustrious researchers, including Stork, House and Corey. Despite this, its synthesis is a much more rewarding proposition than that of the more elaborate parent acid (2), which contains the additional inconvenience in its possession of the extra 13α-hydroxyl and $\Delta^{1,2}$-olefinic functionalities. Indeed, it is only recently that suitably substituted gibberellin synthons have been prepared for future modification to gibberellic acid (2) by the work of Mander[2] and Corey[3,4].

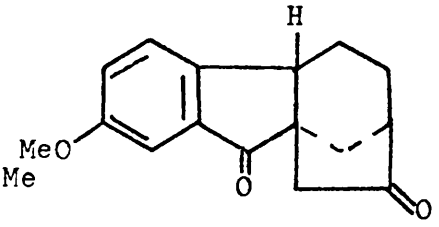
From early degradative studies it became apparent that ring A of the gibberellins was extremely sensitive to hydrolytic conditions, with the epimerisation of the 3β-hydroxyl group by a retro-aldol mechanism or even aromatisation[5,6,7]. Accordingly, this labile portion of the gibberellins is constructed either in the ultimate sequences of the synthesis or at its inception, in the protected form of an aromatic precursor. Such a precursor must possess functionality suitably disposed for the future conversion to ring A of gibberellin A4 as inferred by Loewenthal[8,9] who used 5,6,7,8-tetrahydro-2-methoxynaphthoic acid as a model. Reductive methylation, followed by lactonisation of the acid, produced the keto-lactone (3) in excellent yield. The analagous $\Delta^{1,2}$-olefinic lactone as a ring A equivalent of gibberellic acid was also synthesised.

Thus, Loewenthal's research could be complemented by subjection of the diacid (4) to the forementioned reaction conditions to afford gibberellin A4. This diacid has since been prepared independently, and by alternative routes, by Loewenthal[10] and Baker[11], with the former in the process of attempting this conversion. The object of this thesis was to synthesise an appropriate precursor for future elaboration to



(5a) α-CO_2Me

(5b) β-CO_2Me



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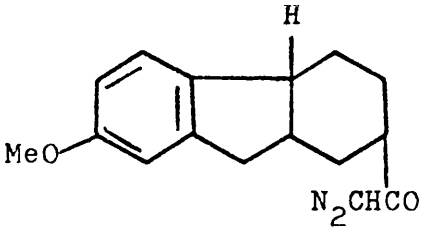

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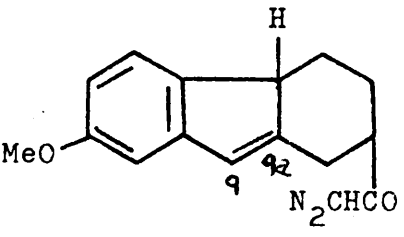

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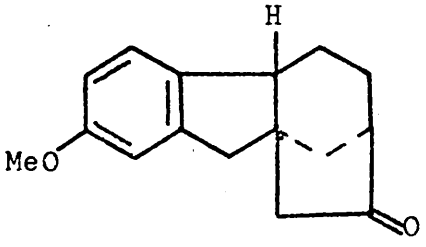

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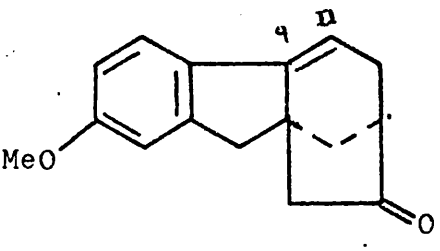


(10)

the diacid (4).

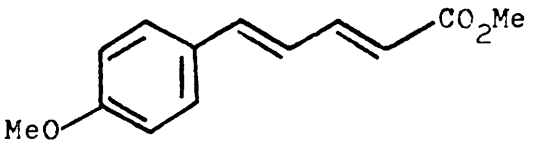
The initial target molecule was the keto-ester (5b) containing the 4aβ-hydrogen atom which would become the 9β-hydrogen atom of any subsequent gibbane. The production of the potential 9β-gibbane hydrogen atom at the inchoation of the synthesis provides an attractive alternative to Loewenthal's[12] lengthy procedure, in which he catalytically hydrogenates $\Delta^{9,11}$-gibbanes; a prerequisite for the stereospecific formation of a 9β-hydrogen atom being the presence of an unnatural 6α-carboxylic acid moiety.

The keto-ester (5b) has the following additional attractions:

a) Previous investigations into the introduction of electrophilic species at the 9a- position of 1,2,3,4,4a(βH), 9a(βH)-hexahydro-9-oxo fluorenes have revealed that the resulting hydrofluorene enolates always react with the electrophile to furnish a 9aβ- analogue. Hence, it should be possible to introduce a 9aβ-acetic acid grouping, which could conceivably undergo an intramolecular Dieckmann cyclisation to provide the gibb-A-triene (6).

b) Failing the Dieckmann approach to the gibbane skeleton, the keto-ester (5b) is ideally constructed for the future modification to the corresponding desoxy diazo ketone (7) or its $\Delta^{9,9a}$-olefinic equivalent (8), which could possibly undergo either an intramolecular keto-carbenoid insertion in the former case, or the increasingly popular nucleophilic displacement of nitrogen in the latter case; two reaction classes which appear with almost quotidian regularity in the current literature. The advantage in the reaction of the desoxy-diazo ketone (7) lies in the retention of the preformed 9β-hydrogen atom in the resultant gibb-A-triene (9), while the diazo keto-olefin (8) would afford the less elaborate keto-olefin (10) requiring the introduction of a 6α-carboxylic acid unit to afford the 9β-hydrogen atom on catalytic hydrogenation, as stated by Loewenthal[12].

c) Having attained the synthons (6), (9) or (10), the introduction of the 4- and 6-carboxylic acid functionalities should be straightforward since their insertion into 3-methoxygibb-A-trienes and 3-methoxy-9-oxo-gibb-A-trienes



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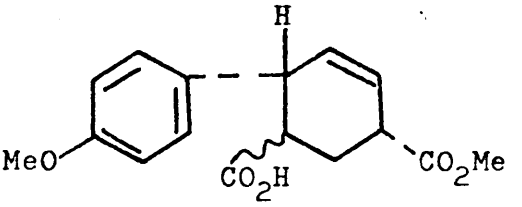
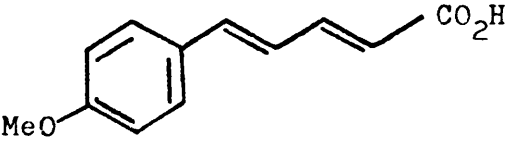


(12a)α-CO_2H

(12b)β-CO_2H



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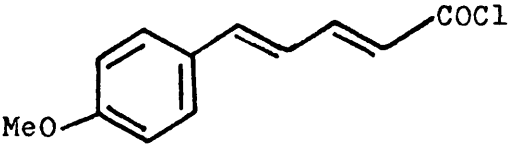

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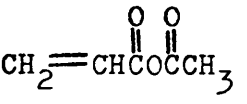


(15)

is well established, with the conversion of the diketone (6) into the diacid (4) already having been perfected by Baker[11].

Thus, an efficient, highly stereoselective route to the hydrofluorenone (5b) was required, conceivably originating from a regiospecific and stereoselective Diels Alder cyclisation between methyl-5-(p-methoxyphenyl)-trans, trans-2,4-pentadienoate (11) and acrylic acid to afford the acid-ester (12a), which, following catalytic hydrogenation of the $\Delta^{3,4}$-olefin, could undergo an intramolecular Friedel Crafts acylation on the corresponding acid chloride to provide the target molecule (5b), after epimerisation of the resultant 2α-carbomethoxy function in the keto-ester (5a).

The method of choice for the construction of the cyclohexane ring with stereochemical control over the functionalities was the Diels Alder cyclisation[13,14,15]; a reaction named after its discoverers, who won the Nobel Prize for chemistry in 1950. In general, the products obtained from the reaction may be formulated with reference to three rules elucidated by Alder and Stein[16]:

a) The diene, in the cisoid conformation, combines with the dienophile to yield a six-membered ring product.

b) A cis addition principal is operative, with the relative orientation of the groups in the diene and dienophile being preserved in the final product.

c) The endo addition rule, which involves the two reagents being preferentially orientated in the endo configuration, is adhered to.

If the "Principal of maximum overlap of non-bonding orbitals", the "Woodward-Hoffmann generalised selection rules for pericyclic reactions", or the "Mobius-Huckel concept in concerted reactions", are operative[17,18,19], then the diene ester (11) and the dienophile, acrylic acid, should align themselves as closely as possible, with the anisyl grouping of the diene and the conjugated acid group of the dienophile overlapping each other. Only with this orientation will the most thermodynamically favoured transition state be formed, which, followed by conrotation of the diene with concomitant bond formation, should afford the acid-ester (12a) in a regiospecific and stereoselective

manner via the $[\pi^4_s + \pi^2_s]$ thermally permitted process.

Condensation of p-methoxybenzaldehyde and methyl crotonate[20] in a t-butanol/potassium-t-butoxide solution produced a mixture which consisted of the diene-ester (11) and the diene-acid (13). On saponification of this mixture, followed by iodine treatment[21], pure diene-acid (13) was obtained as a single isomer as confirmed by n.m.r. spectroscopy.

Acid catalysed methanolysis of the mixture of dienes (11) and (13) afforded, after iodine treatment[21], pure diene-ester (11), while pyridine catalysed thionyl chloride treatment of pure diene-acid (13) produced the corresponding dienoyl chloride (14) as a single isomer as confirmed by n.m.r. spectroscopy.

In this work all asymmetric products described are racemic mixtures. Only one enantiomer is drawn for each; nomenclature is for the depicted enantiomer.

A summary of the Diels Alder reactions is provided on page 29. When the Diels Alder reaction of the diene-ester (11) and acrylic acid was performed in either refluxing xylene or toluene a 1:1 mixture (by g.l.c. analysis) of the cis- and trans- epimeric acid-ester, (12a) and (12b) respectively, was obtained in a regiospecific manner. However, if warm (50°) benzene was used as solvent, the sole crystalline product isolated after 21 days was the acid-ester (12a); the reaction being regio- and steriospecific in this case towards the formation of crystallisable product with only 5% of the trans- epimer (12b) being detected in the resultant mother liquor.

The correlation between the increase in reactivity in a series of dienophiles with dienes in the Diels Alder reaction with a corresponding increase in electron withdrawing substituents in the dienophile has been quite a common observation[22]. In particular, the ability of Lewis acids to activate carboxylic dienophiles has been recognised[23].

It was hoped that these findings could be corroborated by effecting the Diels Alder cyclisation in a warm benzene-acetic anhydride (50°) medium, where the in vitro formation of the mixed anhydride (15) would activate

DIELS ALDER REACTIONS

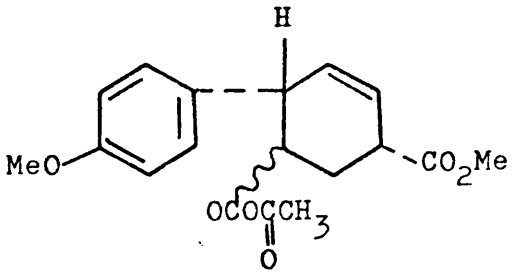
DIENE (Ref.No.)	DIENOPHILE	CONDITIONS Temp./Solvent/Time	CIS:TRANS RATIO (Isolated Product Mixture)	ISOLATED PRODUCT YIELD(%)
			(12a):(12b)	
(11)	ACRYLIC ACID	138°/XYLENE/24h	1:1	90
		111°/TOLUENE/24h	1:1	80
		81°/BENZENE/4days	4:1	85
		50°/BENZENE/21days	100% CIS	45
		50°/BENZENE-ACETIC ANHYDRIDE/4days	1:1	70
			(17a):(17b)	
(11)	METHYL ACRYLATE	81°/BENZENE/14days	13:7	10
		81°/METHYL ACRYLATE/10days	7:3	25
		18°/METHYLENE CHLORIDE/24h[1].	3:2	80
		18°/METHYLENE CHLORIDE/24h[2].	13:7	45
			(18a):(18b)	
(14)	ACRYLYL CHLORIDE	100°/neat/2days	17:3	85
		76°/neat/4days	100% cis[3].	95
			(18a):(18b)	
(13)	ACRYLYL CHLORIDE	100°/neat/4days	3:1	85
			(18a):(18b)	
(13)	ACRYLIC ACID	81°/BENZENE/14days	1:1	8
		142°/ACRYLIC ACID/6days	1:1	2

All epimeric ratios were determined on recrystallised solids or oils, in the case of (17a) and (17b), obtained after work up, by g.l.c. analysis of the corresponding esters, prepared from diazomethane.

1. The dienophile was pre-stirred in a methylene chloride/aluminium chloride suspension at -30°.

2. The diene was pre-stirred in a methylene chloride/aluminium chloride suspension at -30°.

3. Analysis of the mother liquor revealed a 87:13 mixture of epimeric diacids (18a) and (18b), in favour of the former.



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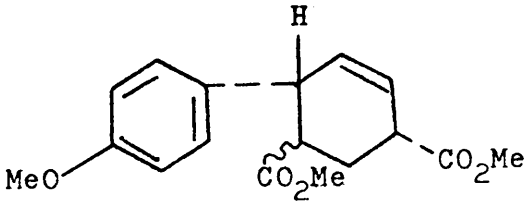
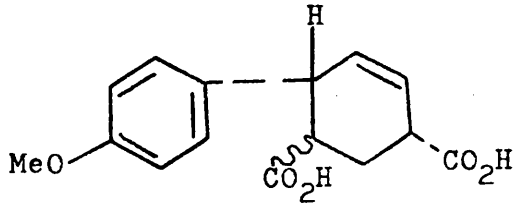
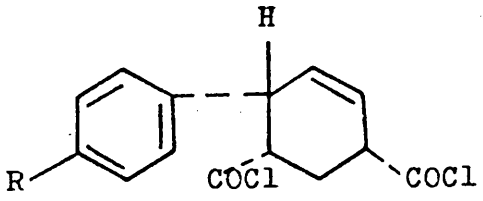


(17a)α-CO_2Me
(17b)β-CO_2Me



(18a)α-CO_2H
(18b)β-CO_2H



(19) R=H
(20) R=OMe

the acrylic acid with a resultant decrease in the duration of the process, yet maintaining the stereospecific nature under the relatively low temperatures employed, compared to the refluxing toluene, which afforded an epimeric mixture of acid-esters (12a) and (12b). The fact that increasing the electrophilicity of the dienophile by the formation of the mixed anhydride (15) (identified by infra red spectroscopic analysis of the residue produced from a high vacuum distilled aliquot) occurred with a concurrent increase in the reaction rate was observed, however, was detracted by the accompanied loss of stereoselectivity, since a 1:1 mixture of the two epimeric acid-esters, (12a) and (12b), resulted. Suspecting that possibly only the cis-epimer (12a) was formed during the reaction, and was later epimerised to the trans epimer (12b) under the reaction conditions, a sample of acid-ester (12a) was subjected to identical reaction conditions. This postulate, however, was shown to be bogus since the only product obtained from the reaction was unepimerised starting material (12a). In every experiment involving the presence of acetic anhydride, no trace of any mixed anhydrides (16) was detected in the products, despite their obvious presence during the reaction, presumably resulting from their hydrolysis under the aqueous conditions applied on work up.

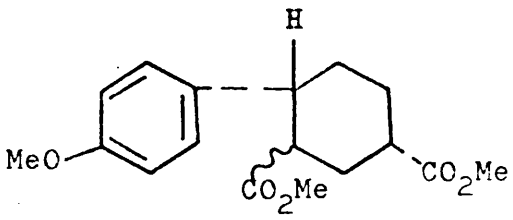
The electrophilicity of the dienophile was increased by using methyl acrylate as an alternative for acrylic acid. When the Diels Alder reaction was conducted with this dienophile and the diene-ester (11) in the presence of either refluxing benzene or methyl acrylate, an epimeric mixture of the diesters (17a) and (17b) resulted. As recorded previously, the reaction was stereoselective, with a 2:1 mixture of the diesters being produced in favour of the cis-epimer (17a). The activity of the dienophile was further increased by pre-stirring it in the presence of aluminium chloride, but, as in the acrylic acid/acetic anhydride case, this reduced the stereoselectivity to a 3:2 mixture of the diesters in favour of the cis-monomer (17a), despite the lowering of the reaction temperature (methylene chloride stir at room temperature).

Having examined the formation of the diesters (17a) and (17b) and the acid-esters (12a) and (12b), then the study of the diacids (18a) and (18b) was an obvious topic for research. The Diels Alder cyclisation between the diene-acid (13) and acrylic acid in either refluxing benzene or acrylic acid was discouraging, with a 1:1 mixtureof epimeric diacids (18a) and (18b) being produced in each case.

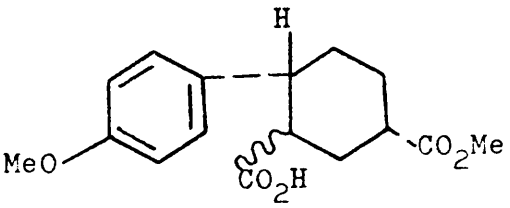
A more promising mode of attack was based upon the earlier observation by Alder[24], who isolated the all cis diacid chloride (19) in excellent yield from the reaction between 5-phenyl-trans,trans-penta-2,4-dienoyl chloride and acrylyl chloride at 100° for 3 days, which was regio- and stereospecific. Consequently, it was found that a corresponding treatment of the dienoyl chloride (14) resulted in a 17:3 mixture of epimeric diacids (18a) and (18b), in favour of the cis-epimer (18a), on crystallisation of the crude reaction mixture. When the reaction temperature was reduced to 76° the only crystalline product isolated after recrystallisation was the diacid (18a); the resulting mother liquor being composed of a 87:13 epimeric mixture of the diacids (18a) and (18b), in favour of the former monomer. Alienated from Alder's reaction, no acid chlorides were isolated, with the in vitro conversion of the endioyl chloride (20) to the corresponding endiacid (i8a), as witnessed by the evolution of hydrogen chloride on the addition of aqueous acetone during the reaction work up.

A somewhat incongruous reaction occurred on subjection of the diene-acid (13) to analagous reaction conditions in the presence of acrylyl chloride, where the in vitro formation of the dienoyl chloride (14) should have facilitated an equally productive yield of pure, crystalline diacid (18a). Unfortunately, this route proved unrewarding due to the resulting, inseparable mixture of crystalline diacids (18a) and (18b) in a 3:1 ratio in favour of the former monomer.

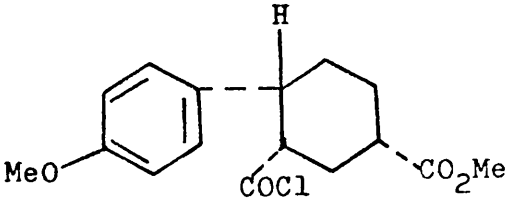
Epimerisation studies on the pure cis-diacid (18a) and cis-diester (17a), in both acidic and basic media, disclosed that each was fairly resistant to epimerisation. In all of the experiments only four compounds were produced:



(21a) α-CO_2Me
(21b) β-CO_2Me



(22a) α-CO_2H
(22b) β-CO_2H



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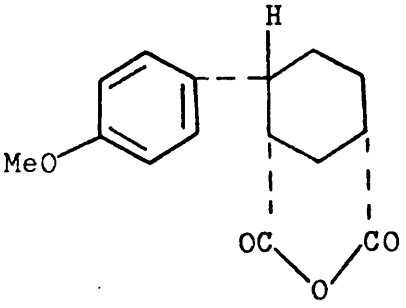

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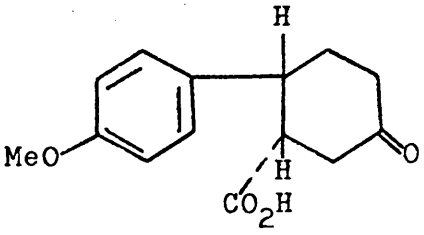

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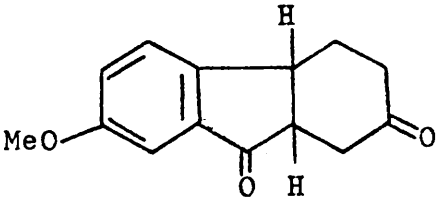

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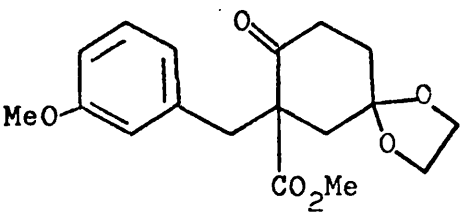

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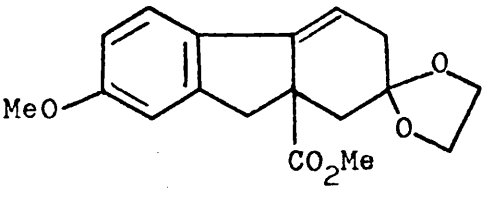


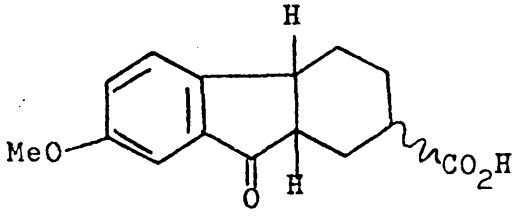
(28)

diacids (18a) and (18b) in the diacid (18a) case and diesters (17a) and (17b), accompanied by the diacids (18a) and (18b), in the case of the diester (17a). No other diastereoisomers were observed.

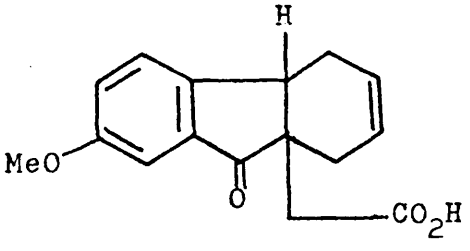
Catalytic hydrogenation of the acids (18a) and (12a) afforded the corresponding cis cyclohexane acids (22a) and (21a) respectively. On subjection of an epimeric mixture of acids (18a,b) and (12a,b) to identical hydrogenation conditions, the corresponding rate of reaction was retarded in some manner due to the presence of the acids (18b) and (12b), which were apparently acting as catalytic poisons towards the hydrogenation of the cis-epimers or were hydrogenated at a much slower rate than that of their cis analogues. The hydrogenated products in each case consisted of an epimeric mixture of acids (22a,b) and (21a,b) in the same isomeric ratio as the reactant acids (18a,b) and (12a,b) respectively.

The conversion of the acid-ester (21a) into its corresponding acid chloride (23), followed by an intramolecular Friedel Crafts acylation reaction, produced poor yields of the hydrofluorenone (5a) (4%), as a single isomer, while polyphosphoric acid treatment afforded the endo-anhydride (24) ($\nu_{max.}$ 1815 and 1771 cm^{-1}) in equally low yields (4%); no hydrofluorene derivatives were observed. In both cases intermolecular reactions appeared to be favoured since the major products were unidentifiable, high molecular weight polymers. This preference for intermolecular coupling can only be attributed to the presence of the 5-carbomethoxy function, especially in the polyphosphoric acid promoted cyclisation reaction, since Ziegler[25] converted the keto-acid (25) into the diketone (26) in excellent yield under similar reaction conditions, although Thompson[26] observed no complications in his internal cyclisation of the keto-ester (27) to the hydrofluorene derivative (28).

Previous studies[27] on the infra red spectra of cyclic anhydrides derived from their corresponding dicarboxylic acids have shown that for unstrained six-membered glutaric anhydrides absorbances occur in the regions 1812 and 1764 cm^{-1} while the analagous succinic anhydrides



(29a) α-CO_2H
(29b) β-CO_2H



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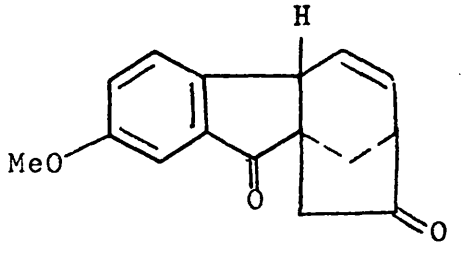

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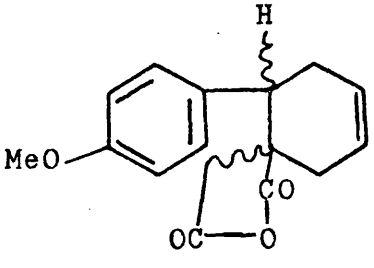
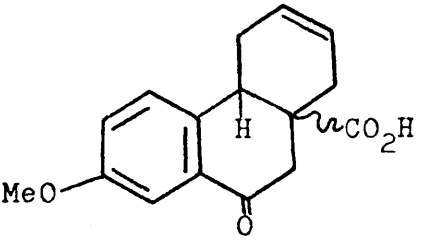
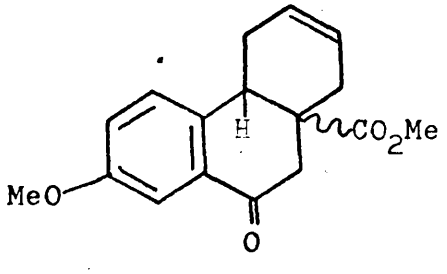


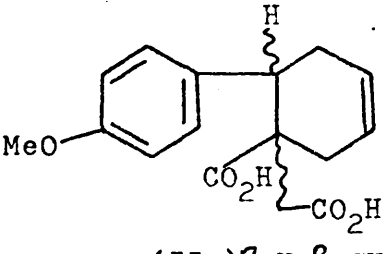
(32a) β-H, β-CH_2CO
(32b) β-H, α-CH_2CO
(32c) α-H, β-CH_2CO



(33)



(34)



(35a) β-H, β-CH_2CO_2H
(35b) β-H, α-CH_2CO_2H
(35c) α-H, β-CH_2CO_2H

absorb in the regions 1860 and 1792 cm^{-1}. Further confirmation concerning the structure of the anhydride (24) originated from its conversion to the keto-ester (5a), via the keto-acid (29a), on treatment with anhydrous aluminium chloride in excellent yield. The purity of the aluminium chloride used was found to be rather critical. When "reagent" grade aluminium chloride was employed the reaction was found to be slow and the yield was erratic. By using triply sublimed aluminium chloride the yield was consistently high and reproducable only when four or more equivalents were added to a stirred, redistilled, anhydrous methylene chloride solution very slowly. The reaction was inhibited if less than 1·5 equivalents was used and was retarded if between 1·5 and 2·5 equivalents was employed. Thus, the serendipitous formation of the anhydride (24) provided an attractive intermediate in the synthesis of the keto-ester (5a) by filling the role of a surrogate precursor vacated by the acid chloride (23).

While the attempted polyphosphoric acid induced cyclisation of the acid-ester (21a) was in progress, Martens[28] had greater success in his cyclisation of the olefinic acid (30) to the gibberellin precursor (31) in the presence of polyphosphoric acid. Thus, it was hoped that polyphosphoric acid treatment of the epimeric mixture of the anhydrides (32a),(32b) and (32c), synthesised as a three stereoisomeric component mixture on the thermolysis of an intimately powder ed mixture of itaconic acid and the diene-ester (11)[20], might produce the forlorn formation of the diketone (31) by the initial regiospecific, aromatic nucleophilic attack on the 1-carboxylic acid grouping in the anhydrides (32), with the consequent in vitro formation of the hydrofluorenone (30), which could then partake in Marten's cyclisation.

However, when these proposals were put into practice, only the hydrophenanthrenone derivative (33) was produced by the regiospecific, nucleophilic attack at the acetic acid grouping in the anhydrides (32). This was not surprising since the formation of the six-membered ring B of the phenanthrene skeleton is favoured over that of the

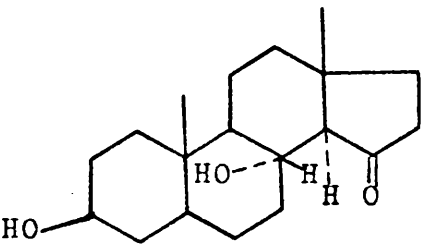
analogous five-membered ring B of the gibberellins by the closer proximity of the aromatic ring A to the acetic acid functionality. This observation of the specific formation of the tetralone in preference to the indanone has been corroborated by previous researchers[29,30].

Attempts at isolating the hydrophenanthrenone from the multi-component gum produced from the polyphosphoric acid reaction proved futile, but on esterification of the gum, the hydrophenanthrenone-ester (34) was isolated as a single isomer whose stereochemistry was left undetermined.

Assignment of the structure (34) was made from the spectroscopic observation that a carbonyl frequency of 1682 cm^{-1} is indicative of a tetralone rather than an indanone (νmax. normally about 1705 cm^{-1}) and if the corresponding indanone had been produced in the reaction medium it would have cyclised to the diketone (31) under the reaction conditions. Further support was forthcoming from the Friedel Crafts cyclisation of the mixture of anhydrides (32) which afforded the forementioned hydrophenanthrenone-ester (34), after esterification and chromatographic purification, in greater yield. An alternative approach to the keto-ester (34) was investigated by subjecting a mixture of the stereoisomeric diacids (35a), (35b) and (35c), produced by the base hydrolysis of the anhydrides (32a), (32b) and (32c), to polyphosphoric acid treatment followed by esterification. As before the only product isolated was the hydrophenanthrenone ester (34).

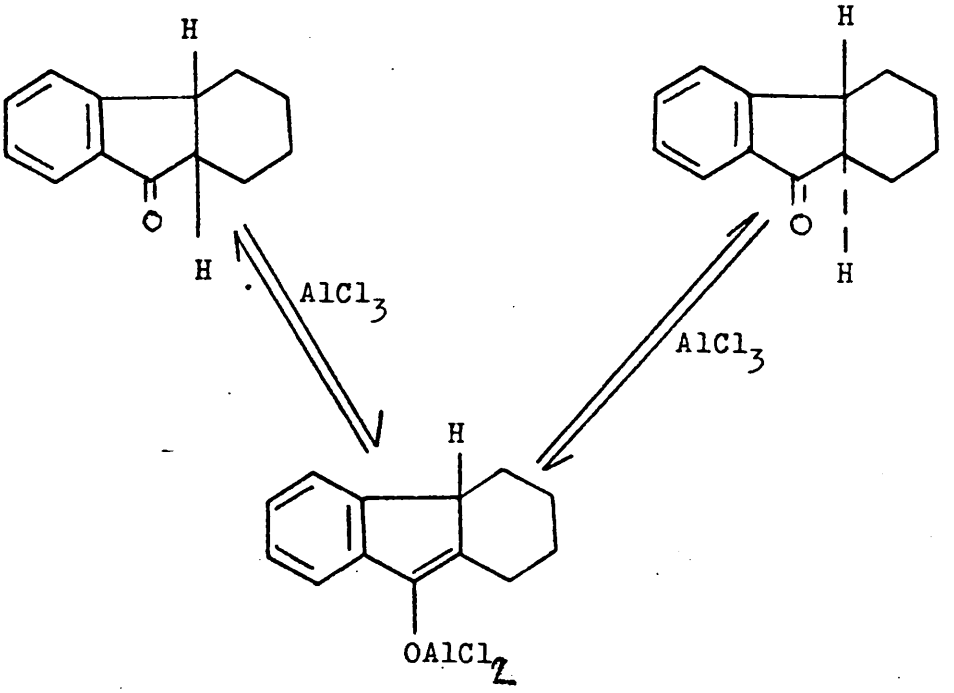
Having followed this innocuous furcation in an attempt at the one-pot formation of the gibbane skeleton, attention was refocussed on a high yielding synthesis of the anhydride (24). Treatment of the diacid (22a) with acetic anhydride at 60^{o} produced in almost quantitative yield the anhydride (24), identical in all respects with that formed by the polyphosphoric acid treatment of the acid-ester (21a).

It was hoped that an epimeric mixture of the diacids (22a) and (22b) would also provide crystalline anhydride (24) on similar treatment by the in situ epimerisation of the trans epimer (22b) to its cis analogue



(36)

SCHEME 1

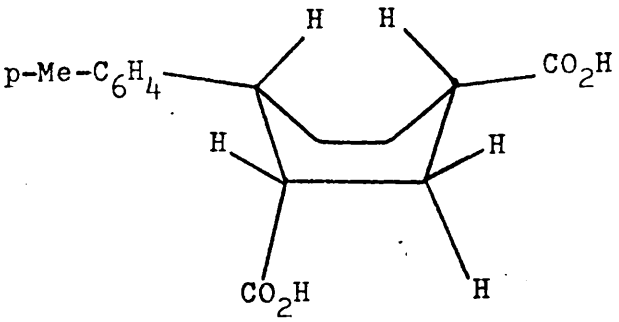


(22a) under the reaction conditions. Unfortunately, this proposal remained as a speculation, since isolable anhydride (24) did not materialise; the products being in the form of an unresolvable mixture of anhydrides, of which the endo-anhydride was a component. The same dicarboxylic acids (22a) and (22b) were recovered upon treatment of this anhydride mixture with hot water, in their original epimeric ratio, indicating that the trans-diacid (22b) had failed to epimerise to the cis-diacid (22a), which was automatically trapped as its anhydride (24) when reacted with acetic anhydride. Thus, this interconversion of the diacid (22a) and the anhydride (24) under non-epimerisable conditions, implies that the two carbonyl functions have a similar configuration.

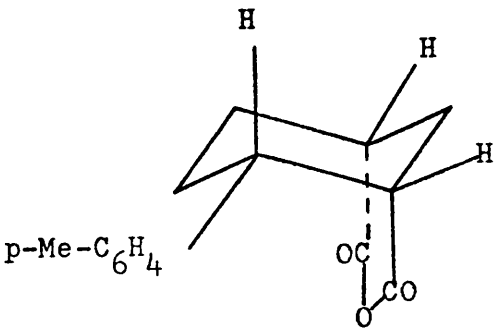
The assignment of the cis-fused BC ring junction in the keto-ester (5a) and the keto-acid (29a) is supported by the studies of House[31], who has investigated hexahydro-9-oxofluorene derivatives and concluded that the cis-fused BC ring junction is always the thermodynamically more stable isomer unless the rigid geometry of the molecule prevents this, as exemplified by the steroid (36)[32]. He also discovered that the formation of hydrofluorenes under Friedel Crafts conditions with aluminium chloride was invariably accompanied by a cis-fused BC ring junction, due to equilibration of the 9aα-hydrogen atom, as depicted in scheme 1.

This equilibration can only occur on the slow addition of aluminium chloride because, if the lewis acid is added quickly, there will be no basic species present to aid the removal of the 9aα-hydrogen atom of any trans-fused BC ring hydrofluorenones produced.

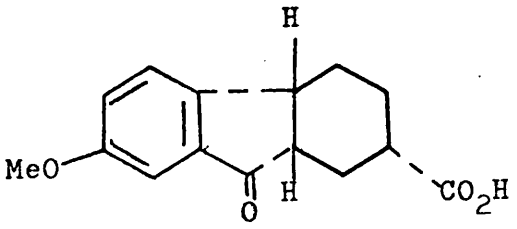
Evidence supporting the 2α-carboxyl functionality in the keto-acid (29a) is provided by the following results:
a) Only one compound was formed in its production from the endo-anhydride (24).
b) The corresponding keto-ester (5a) epimerised to a 1:1 mixture of the keto-esters (5a) and (5b) on subjection to either acidic or basic treatment. Since the molecule (5a) contains only two chiral centres which can be perturbed; the (2) and (9a) carbon atoms, the latter which was formed under



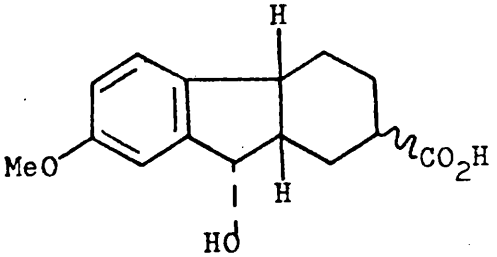
(22a)



(24)



(29a)



(37a) α-CO_2H

(37b) β-CO_2H

equilibrating conditions prescribed by House[31] and is already in its more stable configuration, then the 2-carbomethoxyl site is the only remaining epimerisable centre.

c) The correlation between Alder's findings and the formation of the diacid (22a) implies that the stereochemistry of the cis-diacid (22a) is as shown, with the cis arrangement of the acid groupings being confirmed beforehand by its interconversion with the endo-anhydride (24).

d) The fixed geometry of the epimeric trans-diacid (22b) restricts the formation of a corresponding trans cyclic anhydride. It was also discovered that the epimerisation of the trans-diacid (22b) to the cis-diacid (22a) was impossible under the reaction conditions used in the formation of the endo-anhydride (24).

e) Friedel Crafts treatment of the anhydride (24) would provide the keto-acid (29a), assuming that no epimerisation had occurred at the 2-carboxyl centre in the resultant keto-acid (29a).

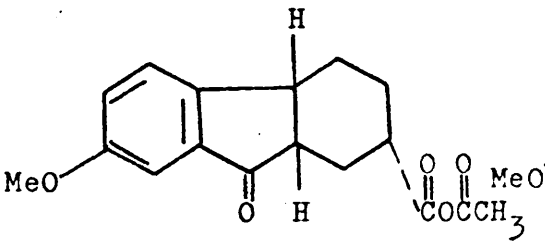
Thus, the epimerisation studies on the keto-ester (5a) implies that the 2-carbomethoxyl function has no preferential orientation in the molecule, in conjunction with the fact that only one isomer was produced from the Friedel Crafts treatment of the anhydride (24), must imply that the acid functionality has remained unepimerised after the formation of the 2α-carboxyl grouping, which is a direct consequence of the rigid geometry inherent to the endo-anhydride (24).

The viability of the intramolecular cyclisation was slightly tainted due to the co-formation of small amounts of the diacid (22a) which co-crystallised with the keto-acid (29a). Resulting from abortive attempts at isolating the keto-acid (29a) in its uncontaminated form by repeated recrystallisations, purification was achieved by the following three techniques:

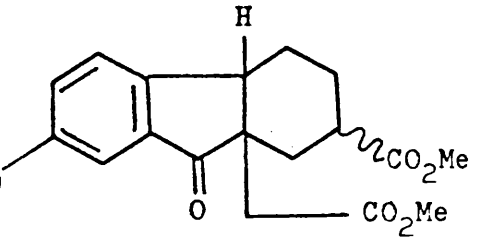
a) Column chromatography.

b) Reduction of the intimate mixture to afford the hydroxy-acid (37a), which crystallised free of contamination, and was then oxidised to regenerate pure keto-acid (29a).

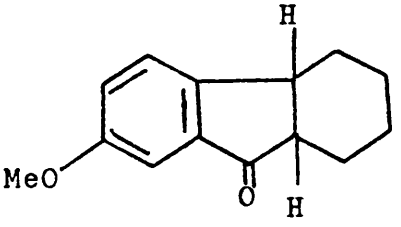
c) Recyclisation of the intimate mixture of crystalline acids



(38)



(39a) α-CO_2Me
(39b) β-CO_2Me



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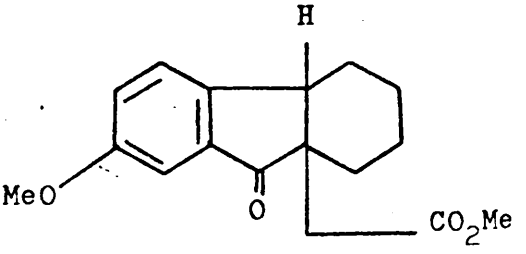

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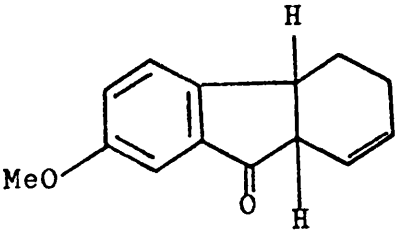

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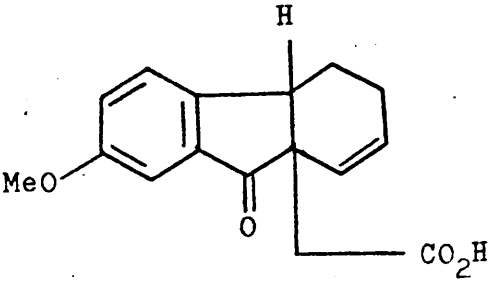

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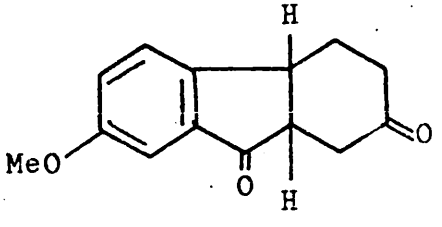

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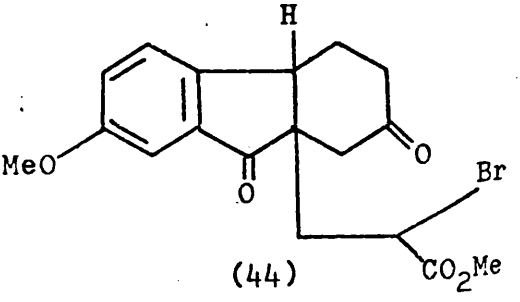


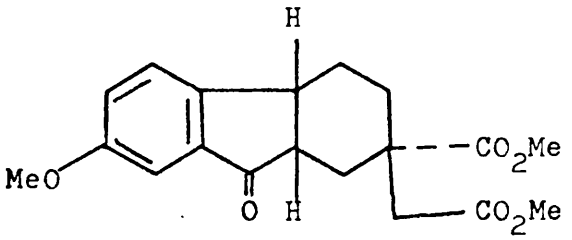
(44)

(29a) and (22a) to reform the anhydride (24), in the presence of the mixed anhydride (38), followed by treatment with aluminium chloride, produced, as before, an intimate mixture of the two crystalline acids (22a) and (29a), enriched in the latter to such an extent that pure, keto-acid (29a) was obtained on recrystallisation.

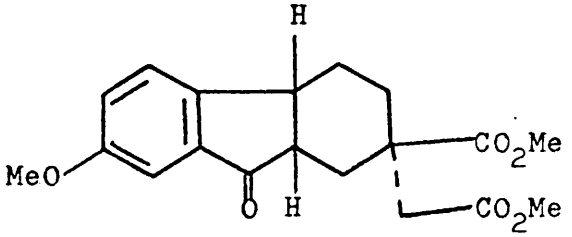
Having obtained the initial target molecule in its epimeric form (5a) in excellent yield, the synthesis of the diester (39b), suitable for Dieckmann studies, was pursued. Treatment of methyl bromoacetate with a preheated solution of the keto-ester (5a) in potassium-t-butoxide/t-butanol effected the introduction of the 9a-methyl acetate grouping as a 1:1 mixture of keto-diesters (39a) and (39b) and the keto-esters (5a) and (5b). The stereochemistry of the 9a-carbon atom can be designated as indicated since House[33] has shown, that for analogous cases, the electrophile always approaches from the less sterically hindered β-face of the enolate anion to produce the corresponding cis-fused BC ring junction: as exemplified by the conversion of the ketone (40) into the keto-ester (41); the ketone (42) into the keto-acid (43)[34]; and the ketone (26) into the bromo-ketone (44).

Thus, carbon atom-(2) must be responsible for the epimerisation to afford the epimeric keto-diesters (39a) and (39b). The keto-esters and keto-diesters were isolated by chromatography and g.l.c. analysis revealed that each consisted of a mixture of epimers (epimeric at carbon-(2)): the epimeric ratio for the keto-diesters (39a) and (39b) being 3:2 in favour of the less polar monomer, and 1:1 for the keto-esters (5a) and (5b). The configuration at carbon atom-(2) for each keto-diester epimer (39a) and (39b) was unassigned.

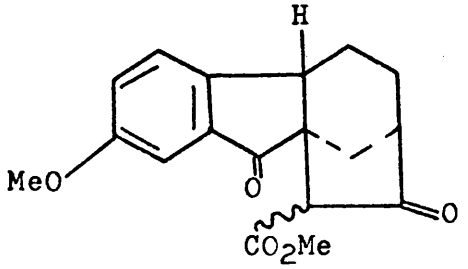
Suspecting that the 3:2 ratio was the equilibrium value for the interconversion of the keto-diesters (39a) and (39b), each epimer was isolated from the monomeric mixture and exposed to butoxide/butanol treatment. Analysis confirmed this prediction in both cases, since the pure keto-diester, (39a) or (39b), afforded a mixture which was composed of the two monomers (39a) and (39b) in a 3:2 ratio, in favour of the less polar epimer. Each epimer (39a) and (39b)


H
MeO
O
H
CO_2Me
CO_2Me

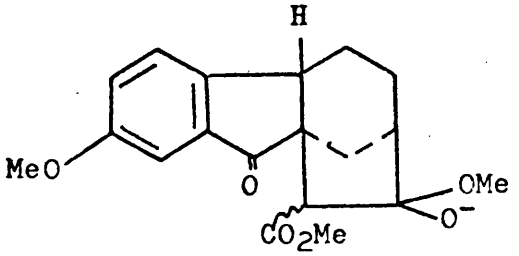
(45)


H
MeO
O
H
CO_2Me
CO_2Me

(46)


H
MeO
O
O
CO_2Me

(47)


H
MeO
O
OMe
O^-
CO_2Me

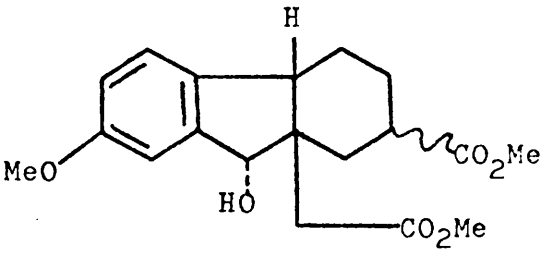
(48)

had almost superimposable spectroscopic properties, with an epimeric mixture of the keto-diesters (39a) and (39b) recording the correct elemental analysis. The epimerisation studies also validated the structure of the keto-diesters as (39a) and (39b) and not the non-epimerisable isomeric keto-diesters(45) and (46).

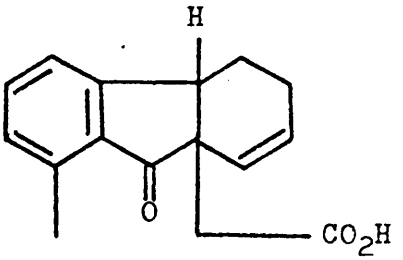
It was expected that a Dieckmann cyclisation of the keto-diesters (39a) and (39b) would afford the β-keto-ester (47) and that its removal from the equilibrating mixture, by the formation of its stable enolate salt, would provide sufficient thermodynamic driving force for the cyclisation. Repeated subjection of an epimeric mixture of the keto-diesters (39a) and (39b) to Dieckmann conditions proved nugatory towards the formation of any tetracyclic material. A similar lack of success resulted when the Dieckmann studies were duplicated on the individual epimers (39a) and (39b). The major product in every experiment consisted of an unidentifiable polymer, accompanied by an epimeric mixture of the keto-diesters (39a) and (39b) in the ratio 3:2 in favour of the less polar monomer.

The only conceivable explanation must lie in the inherent strain of the tetracyclic intermediate (48) produced from the Dieckmann cyclisation. Since the Dieckmann products are formed under reversible conditions, then the intermediate alkoxide (48)must have reverted to the original keto-diester (39b) in order that the strain exerted by the bicyclo(3.2.1)octanone system attached to a cyclopentanone ring could be alleviated. It can also be assumed that the epimer containing the cis configuration of the two ester groupings is always present in the reaction medium since the keto-diesters (39a) and (39b) were epimerised in basic media. Only with this cis configuration will the geometry of the keto-diester be conducive to Dieckmann cyclisation. Thus, the configuration of the keto-diester is immaterial and cannot account for the molecule's inability to undergo the Dieckmann cyclisation.

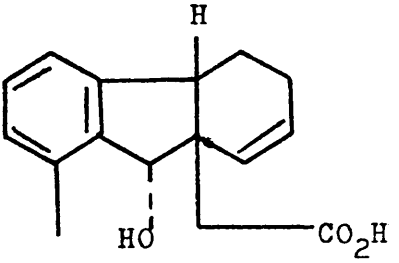
In an attempt at expiating the situation by the alleviation of the inherent strain produced in the intermediate (48), the hybridisation of the C-9 carbon atom



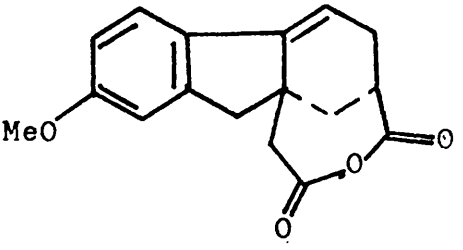
(49a) α-CO_2Me
(49b) β-CO_2Me



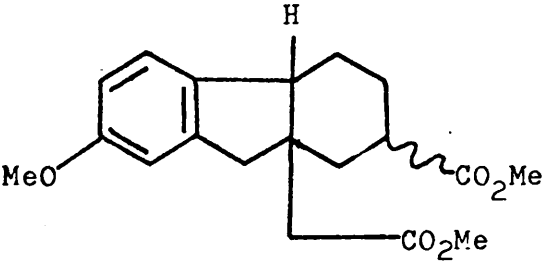
(50)



(51)



(52)



(53a) α-CO_2Me
(53b) β-CO_2Me

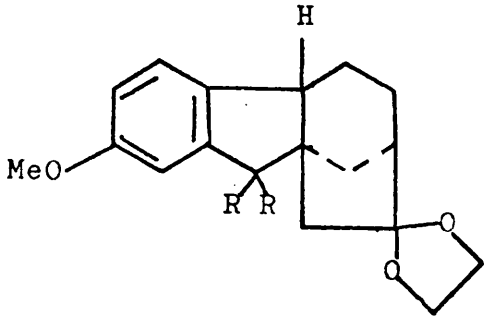
was increased from sp^2 to sp^3 by the stereospecific reduction of the epimeric mixture of keto-diesters (39a) and (39b) to the corresponding mixture of epimeric α-hydroxy-diesters (49a) and (49b). Although the configuration of the hydroxyl grouping was not determined, the literature substantiates the approach of the reducing agent from the less sterically hindered β-face of the keto-diesters (39a) and (39b), to afford the designated epimeric mixture: in his intensive work in this aspect, House[34,35] has never witnessed the attack of the reducing agent from the α-face as exemplified by the conversion of the keto-acid (50) into the α-hydroxy-acid (51).

A mixture of the epimeric hydroxy-diesters (49a) and (49b) formed their corresponding metal alkoxides when subjected to a variety of Dieckmann cyclisation conditions. The alkoxide mixture was precipitated from the reaction media in the form of a white solid and in doing so, nullified any possibility for the formation of any cyclised products.

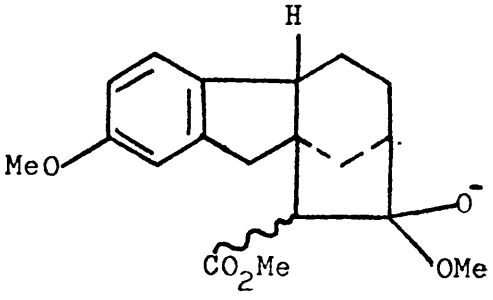
Resulting from abortive attempts at achieving an accurate elemental analysis on the hydroxy-diesters (49a) and (49b), an interesting side reaction of the hydroxy-diesters was discovered: in an attempt at preparing the corresponding acetate, the formation of the olefinic anhydride (52) was forthcoming on treatment of the hydroxy-diesters (49a) and (49b) with warm acetic anhydride.

Alternative analogues of the keto-esters (39a) and (39b) are the diesters (53a) and (53b), which were procured as an epimeric mixture (at C-2) by the catalytic hydrogenolysis of an epimeric mixture of the hydroxy-diesters (49a) and (49b), separable by chromatography. In the reaction of the dimethyl esters (49a) and (49b), methyl acetate, rather than ethyl acetate, was employed as solvent in order to prevent trans-esterification.

Previously, Baltzly[36] reported that all aryl alkyl ketones and secondary alcohols completely substituted in the α-position were inert to hydrogenolysis at room temperature and pressure in the presence of perchloric acid and paladium/carbon catalyst. This innocuous platitude was generally accepted until Baker[11] proved contrary by hydrogenolysing



(54) R=H, OH / R=O



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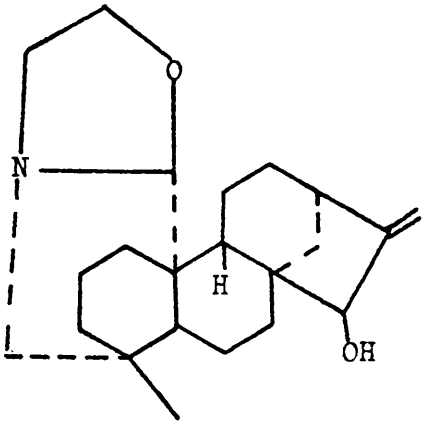

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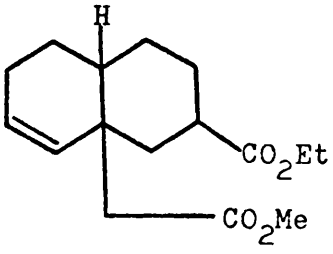

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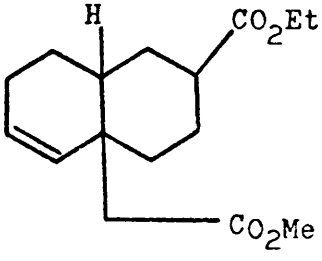

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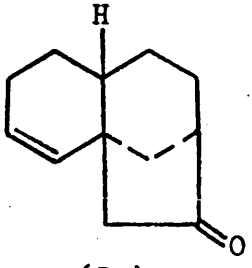

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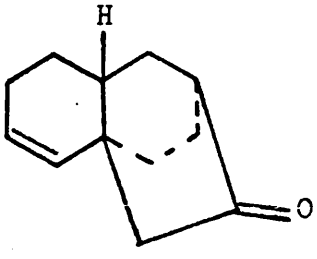


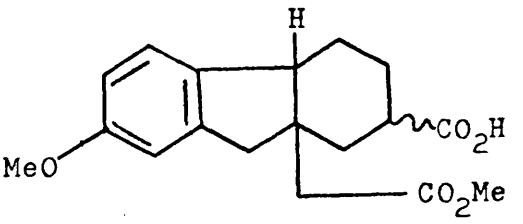
(60)

the ketals (54) to the corresponding 9-desoxy acetates under the previous conditions stated by Baltzly. This corroborates Baker's[30] earlier postulate that the hydrogenolysis reaction procedes via a sp^2 carbonium ion rather than via the olefin formed by the prior dehydration of the alcohol and consequent hydrogenation, as predicted by Baltzly.

Epimerisation studies on each diester epimer (53a) and (53b), in their pure, monomeric states, revealed that each was interconverted to a 2:1 epimeric mixture, in favour of the less polar diastereoisomer. As for the keto- diesters (39a) and (39b), the configuration of the less polar epimer was not assigned. Akin to the keto-diesters (39a) and (39b), when either an epimeric mixture or a pure diester, (53a) or (53b), was subjected to the corresponding Dieckmann cyclisation conditions, the only isolated products were an unidentifiable polymer and an epimeric mixture of the diesters (53a) and (53b).

It appears that even the introduction of a sp^3 hybridised C-(9) carbon atom is insufficient in mitigating the ring strain in the intermediate alkoxide ion (55), which specifically reverts to the original diester (53b) under the reaction conditions in operation.

It is debatable as to whether the attempted cyclisation reactions of the esters (39a),(39b),(53a) and (53b) ever attain the postulated intermediates (48) and (55) since the reaction of hexahydrofluorene-2,9a-diesters under Dieckmann conditions has not been reported in the literature although there is an abundance of information concerning the synthesis of rings C and D from Dieckmann reactions, prior to the construction of ring B. The only analogy provided by the literature concerns the studies of Finnegan and Bachmann[37,38], who have been investigating synthetic pathways to kauranes and atisine (56) by the pre-formation of the BCD ring complex, effected by Dieckmann cyclisations of the diesters (57) and (58) respectively, to produce the corresponding precursors (59) and (60). In both cases, the formation of the tricyclic enones (59) and (60) occurred in only moderate yields under vigorous conditions: refluxing toluene containing sodium methoxide.



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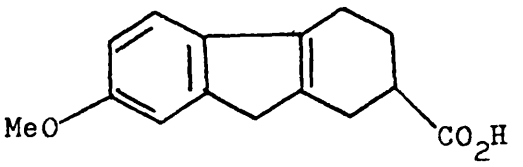

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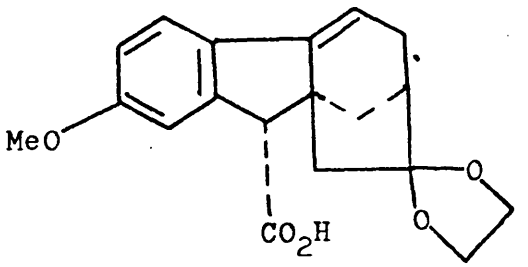

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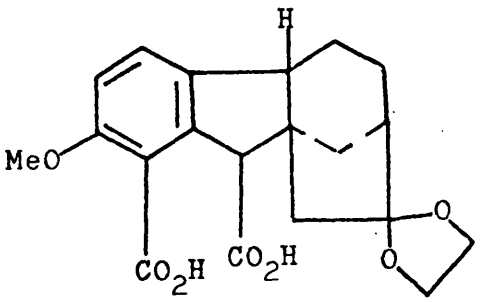

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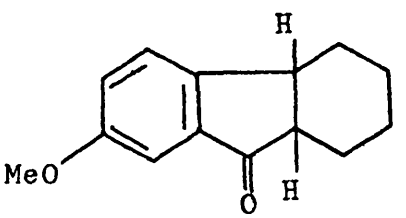

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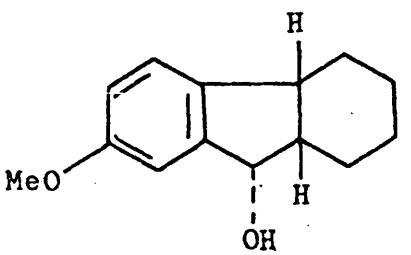


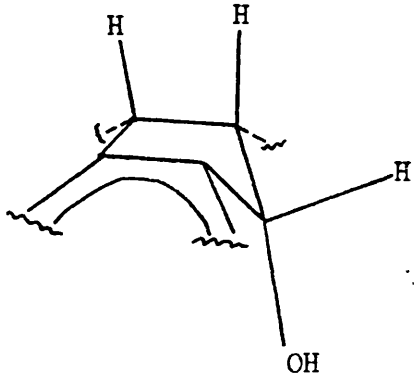
(64)

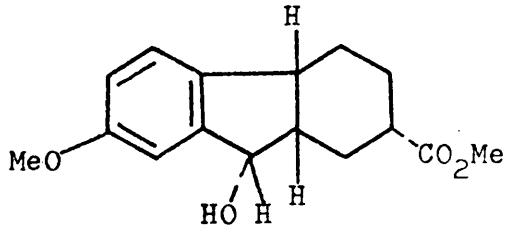
Originating from the inability of the diesters (53a) and (53b) to provide an acceptable elemental analysis, the acid-ester (61) was formed from the selective base hydrolysis of an epimeric mixture of the diesters (53a) and (53b). Chemical evidence substantiating the structure (61) and not the isomeric 2-carbomethoxy-9a-acetic acid derivative, was afforded by the reaction between the keto-acid (29a) and methyl bromoacetate, in the presence of potassium-t-butoxide/ t-butanol, which resulted in moderate yields of the crystalline acid-ester (61) on hydrogenolysis of the crude reaction mixture over Adam's catalyst.

The secondary mode of approach, via the intramolecular cyclisation of diazo ketones, was adopted, since the Dieckmann based route to the gibbane skeleton proved fugacious. The reaction pathway chosen was based upon the pioneering work of Mander[2] and Ghatak[39,40,41,42,43], who provided independent, and alternative, syntheses of 1,2,3,4-tetrahydro-7-methoxyfluorene-2β-carboxylic acid (62) and succeded in its cyclisation, via the corresponding diazomethyl ketone, to the gibba-tetraenone (10). On carbomethoxylation and ketalisation, the ketone (10) should afford the Loewenthal[10] gibberellin precursor (63) by an improved route; the ketal (63) previously having been converted to the gibberellin synthon (4)[10,44].

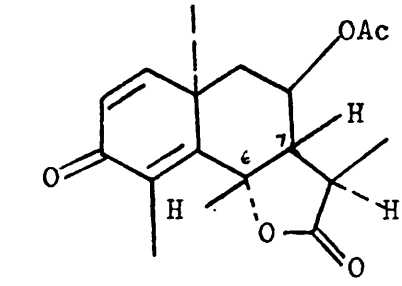
Stereospecific reduction of the keto-acid (29a) with either sodium borohydride or aluminium isopropoxide afforded the hydroxy-acid (37a). By an analogous argument to that used to explain the stereospecific formation of the keto-diesters (39a) and (39b) from the keto-ester (5a), there can be little doubt that the configuration at carbon atom-(9) involves the α-hydroxyl grouping resulting from the approach of the reducing agent from the less sterically hindered β-face of the keto-acid (29a), to produce the α-hydroxyl functionality. This mode of attack is supported by House[33], who has found this to be a common feature in the reduction of cis-fused BC ring hydrofluorenones, as exemplified by the reduction of the ketone (40) to the alcohol (64). This assignment was confirmed by the vicinal coupling constant of 5 Hz between the 9β- and the 9aβ-hydrogen atoms.

STRUCTURE A



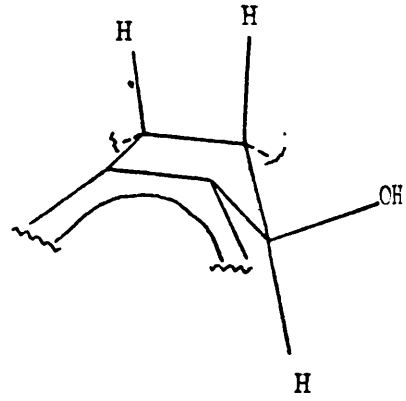


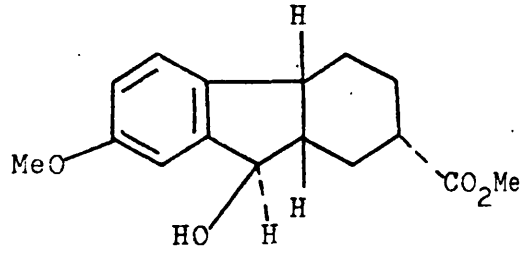
(39a)



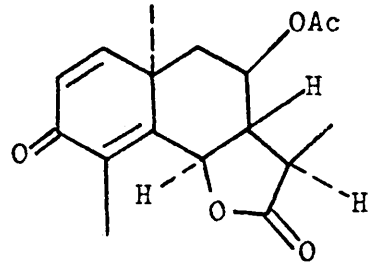
(65)

STRUCTURE B





(39c)



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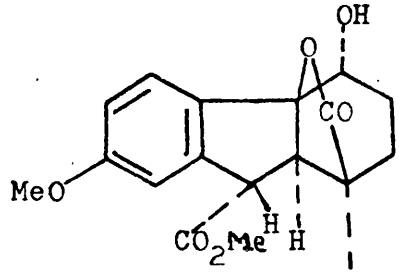

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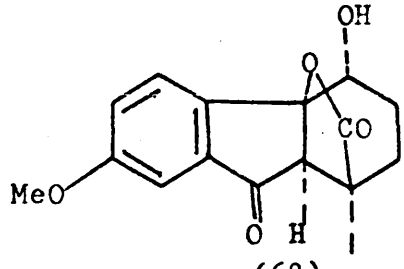
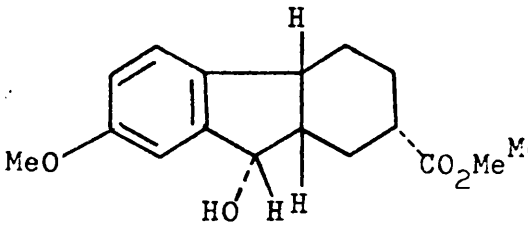


(68)

Karplus[45] has calculated the values of vicinal interproton coupling constants and has shown that they depend on the dihedral angle between the C-H bonds. The magnitude of the coupling also depends on such factors as hybridisation, electronegativities, orientation and bond length of any substituents attached to these carbon atoms as clearly and explicitly outlined by Karplus[46]. Booth[47] discovered that, as a general rule, an electronegative substituent will exert its maximum effect, resulting in a minimum vicinal coupling constant, when an antiperiplanar relationship exists between each part of the coupled pair of protons and the bond by which the electronegative substituent is attached: structure A will exhibit the "Booth" effect, but not structure B. Thus, the effect of the electronegative substituent (the hydroxyl grouping) will be maximised in the 9α-hydroxy- acid (37a) and minimised in the epimeric 9β-hydroxy-acid (37c), with the Karplus value being operative in the case of the latter.

An analogy is provided by the vicinal coupling constant of the santonin derivatives (65) and (66), whose stereochemistry at carbon atoms-(6) and (7) resembles that of the carbon atoms-(9) and (9a) in the 9α- and 9β-hydroxy-acids, (37a) and (37c) respectively. Phiney[48] found that the santonin derivative (66) had a vicinal coupling constant of 11·6 Hz between the hydrogen atoms attached to the carbon atoms-(6) and (7), while its monomer (65) recorded a corresponding vicinal coupling constant of 5·7 Hz. In general, the trans arrangement of the 9- and 9a-hydrogen atoms possesses a greater vicinal coupling constant than the cis arrangement, and this fact was used by Yamada[49] to assign the configuration of the lactone-ester (67), prepared from the ketone (68), as possessing the trans-9β(H)-9aα(H) configuration due to the vicinal coupling constant of 9·2 Hz. Thus, the vicinal coupling exhibited by the trans arrangement of hydrogen atoms in the analogues of the 9β-hydroxy-acid (37c); (66) and (67), imply that the hydroxy-acid isolated from the reduction of the keto-acid (29a) possesses an α-hydroxyl grouping as depicted in (37a).

A similar argument may be used to assign the



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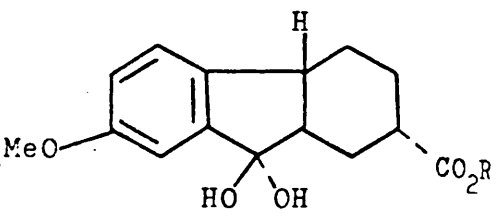
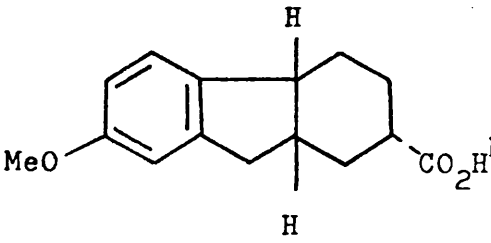
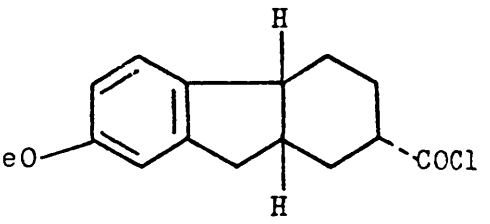


(70) R=H,Me



(71)



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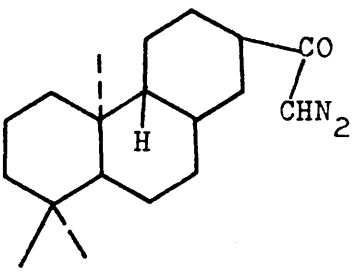

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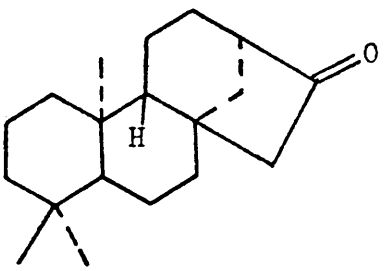

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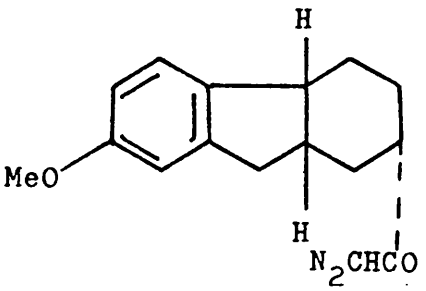
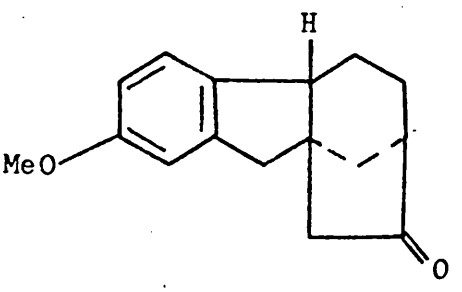


(7a)



(9)

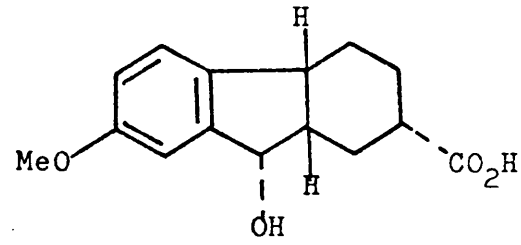
stereochemistry of the hydroxy-ester (69), produced by the sodium borohydride reduction of the keto-ester (5a), which registered a vicinal coupling constant of 5 Hz between the 9β(H) and 9aβ(H) hydrogen atoms.

The reductions of the keto-acid (29a) and the keto-ester (5a) were anomalous in the fact that both reactions necessitated the presence of anhydrous solvents. When the reduction was performed in Analar methanol the reaction was retarded and it was assumed that the formation of the gem diol (70) was responsible, although there was no evidence to support this or explain why the corresponding dimethyl ketal was not formed.

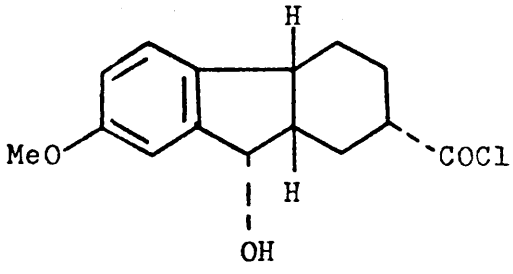
Catalytic hydrogenolysis of the hydroxy-acid (37a) over Adam's catalyst, in the presence of perchloric acid, produced the acid (71) almost quantitatively. Similar treatment of the keto-acid (29a) afforded the same desoxy acid (71) at a reduced rate. A lower yielding production of the acid (71) was effected either by the Clemmenson reduction of the keto-acid (29a) or a Wolff-Kishner reduction: both reactions produced acid (71) possessing similar spectroscopic properties to that produced by the hydrogenolysis reactions despite the difference, and greater range, of melting points, presumably due to the co-formation of its epimeric 2β-acid.

The acyl chloride (72) was produced when the acid (71) was subjected to oxalyl chloride treatment, and afforded the diazo ketone (7a) when stirred in the presence of diazomethane, with or without the presence of triethylamine. The diazo ketone (7a), possessing the characteristic n.m.r. and i.r. bands, was subjected to the intramolecular keto-carbenoid cyclisation conditions used by Yoshikoshi[50] in his conversion of the diazo ketone (73) into the ketone (74), by refluxing in the presence of finely powdered cuprous oxide while illuminated by a 400 watt bulb. Contrary to Yoshikoshi's success, the major product from the reaction was an unanalysable polymer, with no trace of the expected tetracyclic ketone (9).

Elemental analysis of the isolable, crystalline diazo ketone (7a) proved abortive due to its rapid



(37a)



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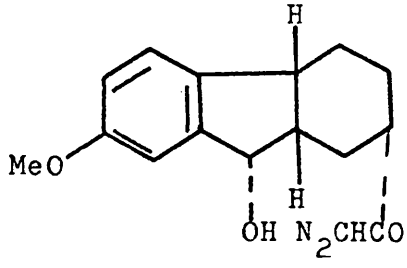

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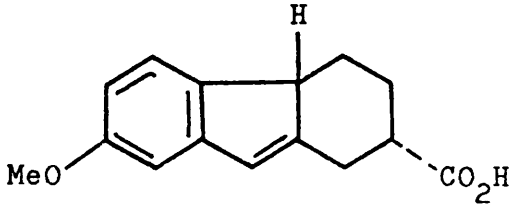


(77)

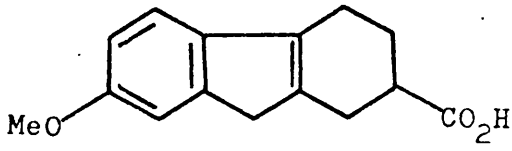
polymerisation, which was only retarded when it was enclosed in an opaque vessel either under vacuum or in a nitrogen atmosphere.

The spin multiplicity of the carbene generated in vitro influences only the chirality, if any, of the resulting product. According to Skell's Theory[51], the triplet carbene reacts via a triplet diradical intermediate, which, before insertion can occur, must undergo a spin inversion, and if free rotation about the carbon-carbon bond of the diradical is faster than the spin inversion, then any chirality possessed by the preliminary carbene is lost. In the case of the singlet carbene, the insertion occurs in a concerted manner with complete retention of any chirality inherent to the carbene. The multiplicity of any carbene generated from the diazo ketone (7a) is immaterial since it must be asymmetric directly at the carbene site. Hoffmann[52] has also confirmed that Skell's Theory is applicable to the insertion reactions of olefinic diazo ketones.

The crude acid chloride (75), obtained from the reaction of the hydroxy-acid (37a) with oxalyl chloride, was reacted directly with an excess of ethereal diazomethane, with or without the presence of triethylamine. The crystalline diazomethyl ketone (76) was subjected to identical intramolecular cyclisation conditions as employed on the diazo ketone (7a), but, as before, the preferential formation of polymer, rather than the desired production of the tetracyclic skeleton, was observed.

The only logical explanation concerning the failures of these intramolecular, keto-carbenoid induced insertion reactions must lie in the unusual instabilities of the diazo ketones (7a) and (76) since the literature is affluent in examples in which polymer formation is non-existent: Ghatak[40,42], Yoshikoshi[50], Agosta[53].

Dehydration of the hydroxy-acid (37a) produced the $\Delta^{9,9a}$-olefin (77) which, based upon the base catalysed isomerisation[33] of 1,2,3,4,4a(βH)-tetrahydro-$\Delta^{9,9a}$-7-methoxyfluorene to the achiral 1,2,3,4-tetrahydro-7-methoxyfluorene, presented an ideal opportunity to



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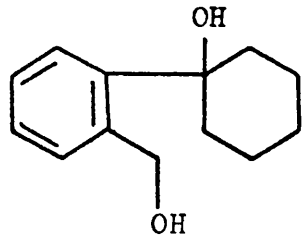

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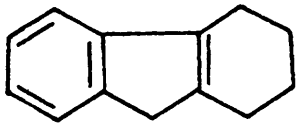

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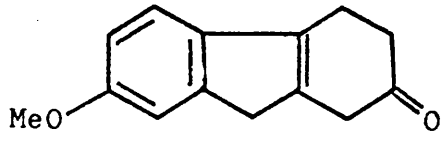
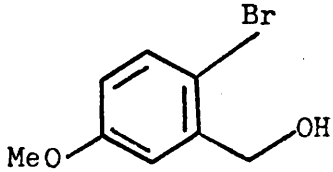


(80)



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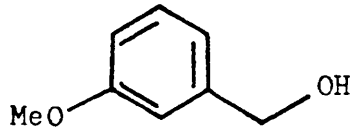

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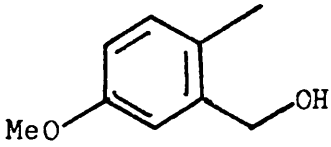

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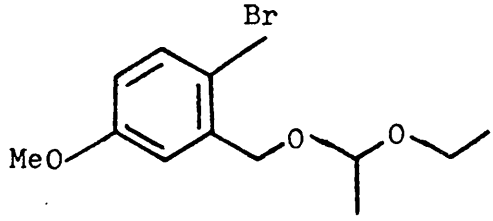

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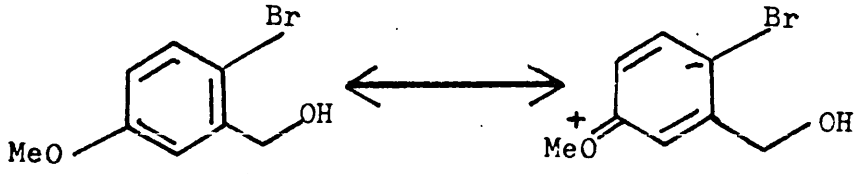


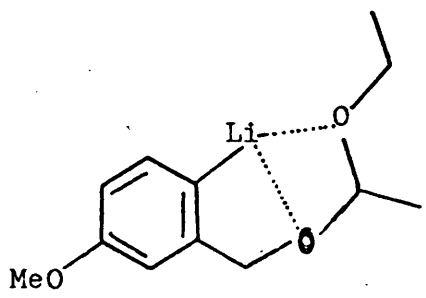
(81) (84)

interrelate this work with that of Mander's. The isomerisation of the olefinic acid (77) produced a racemic mixture of the olefinic acid (62), identical with that prepared by the forementioned researchers[2,43].

An alternative route to the olefin (62), based on the late Parham's indene synthesis, was investigated. Parham constructed the diol (78), from cyclohexanone and o-bromobenzyl alcohol in the presence of n-butyllithium, and then cyclised it to the indene (79) on acid catalysis. It was envisaged that by imitating this reaction with 2-bromo-5-methoxybenzyl alcohol and the monothioketal of 1,4-cyclohexadione, recently prepared by Moss[56], the production of the keto-olefin (80), an ideal precursor for the olefin (62), would be forthcoming.

Subjection of 2-bromo-5-methoxybenzyl alcohol (81) to two equivalents of n-butyllithium, followed by the addition of cyclohexanone, produced starting material (81) and its debrominated equivalent, m-methoxybenzyl alcohol (82), as the sole products. A similar disconsolating result was achieved when acetone was employed as the electrophile; however, when methyl iodide was used, low yields of 5-methoxy-2-methylbenzyl alcohol (83) were isolated. Thus, the reaction appeared to be retarded by the presence of the methoxyl grouping which would destabilise any resulting anion in the molecule, especially at the ortho- and para-sites, by electromerically supplying a partial negative charge into the aromatic ring (84). The feasability of the reactions was at least confirmed by the limited success of the methyl iodide case, in which metal-halogen exchange had occurred.

To stabilise any anionic or lithium-aryl bond formation, the production of the benzylic lithium alkoxide was thwarted by the protection of the benzyl alcohol as its acetal (85), which hopefully could be removed in vitro after the reaction with the electrophile, to facilitate the dehydration step prior to the formation of the indene. This should contribute to the aryl-lithium bond formation by the removal of the adjacent negative charge and also by the



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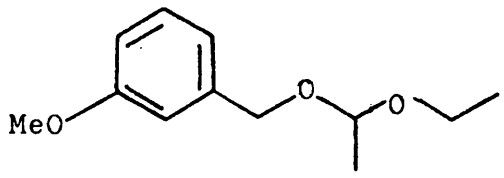
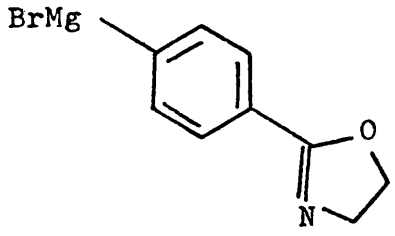


(87)

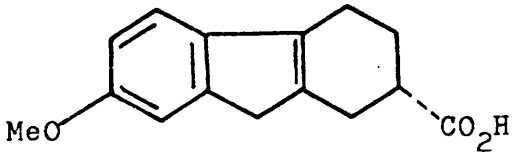


(88)

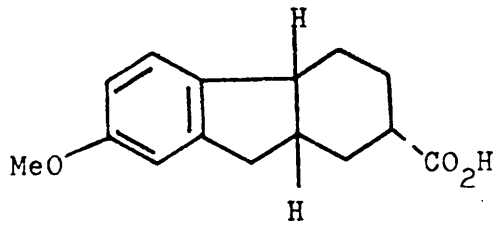
chelation with the lithium metal (86), via the acetal oxygen atoms.

When the electrophilic substitution reactions were repeated on the acetal (85) in the presence of either acetone, cyclohexanone or methyl iodide, the only products were starting material (85) and debrominated acetal (87). No trace of any nucleophilic attack on the introduced electrophiles was noted. Thus, it appears that it requires fairly vigorous conditions to accomplish a bromine-lithium exchange on an aromatic ring containing a para-electron donating substituent.

In an attempt at circumventing the difficulties associated with the previous reactions, the reaction between cyclohexanone and the Grignard reagent prepared from the acetal (85) was investigated. In common with the n-butyl-lithium reactions, this route proved futile, with similar fruitless contributions being provided when acetone or drikold replaced cyclohexanone as the electrophile. In all three experiments the debrominated acetal (87) was produced in greater than 90% yield, indicating the formation of the Grignard reagent; as witnessed by the disappearance of the magnesium metal during the manufacture of the reagent, but whose reaction with introduced electrophiles was prevented in some manner. A possible explanation is provided by Meyers[57], who found that the reaction between N-methylpiperidone and the Grignard reagent (88) was retarded by the nitrogen lone pairs of the electrophile complexing with the magnesium of the Grignard reagent. It appears that an analogous situation exists in the Grignard reagent prepared from the acetal (85), with the intramolecular formation of an acetal oxygen-magnesium complex similar to the chelate (86), resulting in a substantially stabilised reagent in which the acetal functionality prevents the encroachment of any electrophilic reagent. Meyer rectified his problem by complexing the lone pairs of the nitrogen atom in the electrophile with anhydrous magnesium bromide. However, on addition of anhydrous magnesium bromide to the Grignard reaction performed on either cyclohexanone or acetone, the



(62)



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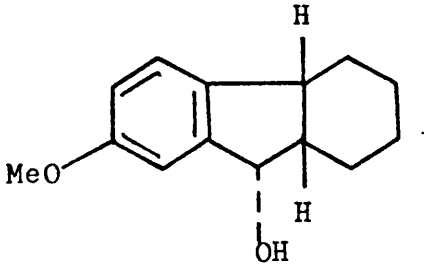
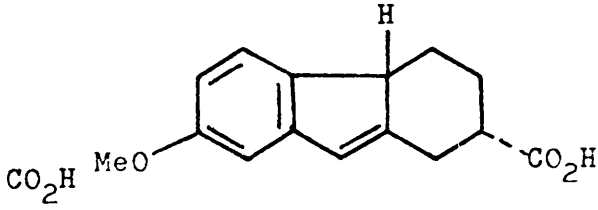


(37a)



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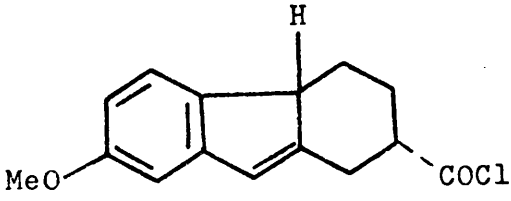

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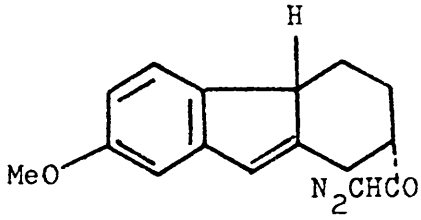
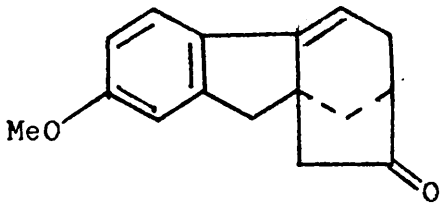


(8a)



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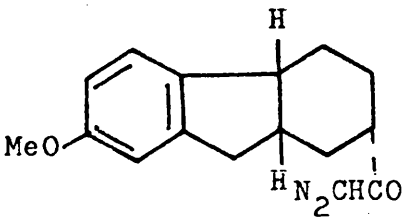
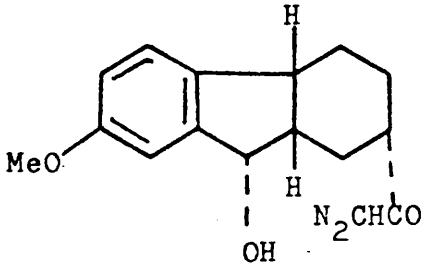


(7a)



(76)

sole product was m-methoxybenzyl alcohol (82); the protecting acetal function having been removed under extremely mild conditions. As expected, the alcohol (81) refused to participate in any Grignard reactions resulting from the precipitation of its metal alkoxide from the non-polar reaction media.

In both the n-butyllithium and Grignard reactions, nucleophilic attack on the introduced electrophiles was non-productive, despite the occurrence of lithium-halogen exchange in the former, and the formation of the Grignard reagent in the latter. The only plausible explanation is that due to the steric inhibition of the acetal-metal complex preventing the approach of the electrophile.

Catalytic hydrogenation of the olefinic acid (62) resulted in the formation of impure acid (71), which refused to register a similar melting point to that of the pure acid (71), prepared by the hydrogenolysis of the hydroxy-acid (37a), despite repeated recrystallisations: 164-168^{o} compared with 170-171^{o} for the pure acid (71). Notwithstanding this discrepancy in melting points, the spectroscopic properties of both acids were almost superimposable, implying the co-existence of the acid (71) and its 4aα(H) epimer. A mixed melting point of 158-164^{o}supports this prediction. This is a rather anomalous situation since it has been noted[26] that, in general, tetrahydrofluorenes are hydrogenated stereospecifically.

The repeated failures of the keto-carbenoid insertion reactions enforced the study of the topical diazo ketone-olefin insertion, or displacement, reaction investigated by the following researchers: Mander[2,58,59,60], Smith[61], White[62], Schleyer[63] and Ghatak[39,42,64]. This reaction can either procede via a singlet or a triplet carbene insertion or nucleophilic displacement of nitrogen; the precise nature of the reaction being variable.

The crude acid chloride (89), produced from the olefinic acid (77), was directly reacted with excess ethereal diazomethane in the absence of triethylamine, to afford the corresponding olefinic diazo ketone (8a). When the diazo ketone (8a) was crystallised and left standing

overnight, it polymerised into a black, acrid tar unless stored under a nitrogen atmosphere in an opaque container. Hence, the crude diazo ketone (8a) was evacuated over silica gel for 30 minutes to remove all traces of solvent and moisture and was then immediately reacted, without further purification, with an excess of boron trifluoride etherate in anhydrous methylene chloride to afford moderate yields of the keto-olefin (10), identical in all respects with that synthesised by Mander[2] and Ghatak[43].

When the reaction was attempted in the presence of trifluoroacetic acid, the reactive solvent favoured by Mander, polymerisation was the major pathway, with no trace of the keto-olefin (10). Irradiation of a solution of the diazomethyl ketone (8a)in a stirred suspension of finely powdered cuprous oxide produced, in common with the diazo ketones (7a) and (7b), polymer.

The simplicity of the approach, the high overall yields in the steps leading to the keto-olefin (10) and the potential adaptability of the route for the synthesis of gibberellins more complex than gibberellin A4 in the original stages of the scheme; especially in the Diels Alder cyclisations of the dienes (11), (13) and (14), where it may be possible to synthesise a potential 13-hydroxylated gibberellin precursor from ethyl α-acetoxyacrylate[2] as a dienophile inplace of acrylic acid acrylyl chloride or methyl acrylate, making this investigation more than just academically interesting.

EXPERIMENTAL.

All melting points were determined on a Kofler microscope hot-stage and are uncorrected.

Liquid film, Nujol mull and solution infrared spectra were recorded on Perkin-Elmer 257 spectrophotometers, while KBr discs were recorded on a Unicam S.P. 1000 or a Perkin-Elmer 225 spectrophotometer by Mrs. F. Laurie and her staff.

Ultra-violet spectra were measured on a Pye Unicam S.P. 800 spectrophotometer as solutions in 95% ethanol.

Nuclear magnetic resonance (n.m.r.) spectra were obtained on Varian T-60 and H.A. 100 spectrometers, using approximately 0·3M solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal standard. Coupling constants (J) were measured in hertz (Hz).

Analytical gas-liquid chromatography (g.l.c.) was carried out on either a Perkin-Elmer F11 Gas Chromatograph with a flame ionisation detector or a Pye Argon Chromatograph equiped with a β-ionisation detector. All compounds were analysed on a 1% OV-1 column.

Thin layer chromoplates were spread with Merck Kieselgel G and preparative chromoplates were spread with Merck Kieselgel HF 254. Column chromatography was carried out on either B.D.H. silica gel for chromatographic analysis 60-120 mesh or on B.D.H. aluminium oxide active, Brochmann grade 1, neutral. Where epimeric mixtures were separated into the constituent monomers, a long, 3cm bore, water cooled column was employed.

Mass spectra were determined on a G.E.C.-A.E.I. M.S.12 spectrometer, where the figure quoted for the molecular ion (M^+) refers to the m/e value, while high resolution mass spectra were recorded using an A.E.I.-G.E.C. M.S. 902 spectrometer.

Drying of organic phases, except where specifically mentioned, was performed with anhydrous magnesium sulphate.

Petrol refers to the petroleum fraction with boiling range 40-60^{o} unless otherwise stated.

All reactions were conducted in either Analar or purified technical solvents[65]. Work ups were carried out using purified technical solvents[65].

Acrylic acid was used immediately after its purification[66].

An excess ethereal diazomethane solution was used to esterify acids for g.l.c. analysis.

All Diels Alder reactions were performed under oxygen-free nitrogen by passing " White spot" nitrogen through an alkaline pyrogallol solution[84].

5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoic acid (13)

This was prepared as described in the literature[30] by the condensation between p-anisaldehyde and methyl crotonate in the presence of t-butanol/potassium-t-butoxide. The resultant mixture of diene-acid (13) and diene-ester (11) was refluxed in methanolic potassium hydroxide overnight to afford diene-acid (13) which was allowed to stand in chloroform for 3 days under a visible lamp, with a few crystals of iodine[21]. Recrystallisation from chloroform gave the pure acid (13) m.p. 182-183° (lit.[30] 182-183°), νmax. (KBr) 1673 cm^{-1}, δ15·5-14·5 (1H,COOH), 7·40 (2H,q, J=9Hz,aryl H), 6·86 (2H,q,J=9Hz,aryl H), 7·6-6·6 (3H,m, vinyl H), 5·90 (1H,d,J=14Hz,2-H) and 3·80 (3H,s,OMe).

Methyl 5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoate (11)

This was prepared as described in the literature[30] by refluxing the diene-acid (13) in dry methanol, containing trace amounts of 98% sulphuric acid, for 4 hours. Recrystallisation from methanol afforded pure ester (11) m.p. 126-127° (lit.[30] 126-127°), νmax. (KBr) 1711 cm^{-1}, δ 7·35 (2H,q,J=9Hz,aryl H), 6·84 (2H,q,J=9Hz,aryl H), 7·6-6·6 (3H,m,vinyl H), 5·90 (1H,d,J=14Hz,2-H), 3·80 (3H,s,OMe) and 3·77 (3H,s,OMe).

5-carbomethoxy-2-(p-methoxyphenyl)-cyclohex-3-en-1-carboxylic acids (12a) and (12b)

a- Preparation using p-xylene as solvent.

A solution composed of the diene-ester (11) (21·8g; 0·1mol), freshly distilled acrylic acid (14·4g; 0·2mol) and hydroquinone (3mg) was refluxed overnight in dry p-xylene (150ml) under a nitrogen atmosphere. Benzene (100ml) was added to the solution, which was then extracted with aqueous sodium bicarbonate. The aqueous extracts

were acidified with dilute hydrochloric acid and extracted with benzene (3 x 75ml). The organic extract was washed with brine, dried and concentrated to afford an orange oil which crystallised on addition of methylene chloride. On recrystallisation from methylene chloride, white crystals of epimeric acid-esters (12a) and (12b) m.p. 90-93° formed. G.l.c. analysis on a sample of this material reacted with an excess of diazomethane revealed a 1:1 mixture of cis (12a) and trans (12b) epimers, (24·1g; 90%).

b- Preparation using toluene as solvent.

A solution composed of the diene-ester (11) (21·8g; 0·1mol), freshly distilled acrylic acid (14·4g; 0·2mol) and hydroquinone (3mg) was refluxed overnight in dry toluene (150ml) under a nitrogen atmosphere. On work up as in a- recrystallisation from methylene chloride afforded a 1:1 mixture of the epimeric acid-esters (12a) and (12b), m.p. 90-93°, (23·2g; 80%).

c- Preparation using benzene as solvent.

A solution composed of the diene-ester (11) (21·8g; 0·1mol), freshly distilled acrylic acid (14·4g; 0·2mol) and hydroquinone (3mg) was stirred under a nitrogen atmosphere for 21 days at 50°. On work up as in a- , recrystallisation from methylene chloride afforded the cis-epimer (12a), m.p. 95-95·5°, exclusively, while analysis of the mother liquor revealed the presence of 5% of the trans-epimer (12b). Analysis of the cis-epimer (12a) gave the following: ν max. (KBr) 1735 cm^{-1} (ester C=O) and 1705 cm^{-1} (acid C=O), λmax. 237 nm (ϵ 13,400), 276 nm (ϵ 1,950) and 283 nm (ϵ 1,760), δ 10·1 (1H,COOH), 7·24-6·84 (4H,q of d,J=9,2Hz,aryl H), 5.98 (2H,m,olefinic H), 3·80 (6H,2 x s,OMe), 3·79 (1H,m, benzylic H) and 2·4-1·9 (4H,m,aliphatic H), (Found: C, 65·95; H, 6·48%, M^+, 290. $C_{16}H_{18}O_5$ requires C, 66·20, H, 6·22%, M^+, 290).

The reaction was repeated by refluxing a solution

of the diene-ester (11) (2·18g; 0·01mol), acrylic acid (1·44g; 0·02mol), hydroquinone (1mg) and benzene (80ml) for 4 days. On work up as before, recrystallisation from methylene chloride afforded a 4:1 epimeric mixture of the acid-esters (12a) and (12b) in favour of the former, m.p. 91-94·5°, (2·4g; 85%).

d- Preparation using benzene-acetic anhydride as solvent.

A solution of the diene-ester (11) (2·18g; 0·01mol), acrylic acid (1·44g; 0·02mol), hydroquinone (1mg), acetic anhydride (5ml) and benzene (75ml) was stirred for 3 days under a nitrogen atmosphere at 50°. On high vacuum distillation of a reaction aliquot, a crude, orange oil was left (νmax. 1815, 1770 cm^{-1}). Analysis of the distillate revealed a complex mixture of anhydrides (νmax. 1835-1805, 1715-1765 cm^{-1}).

On work up as in a- , and recrystallisation from methylene chloride, a 1:1 epimeric mixture of the acid-esters (12a) and (12b), m.p. 90-93°, was obtained (2·0g; 70%).

Reaction of the cis-acid-ester (12a) under the reaction conditions employed in d-.

A solution of pure acid-ester (12a) (1g), acrylic acid (2ml), hydroquinone (1mg), acetic anhydride (4ml) and benzene (50ml) was stirred overnight at 50° under a nitrogen atmosphere. Benzene (55ml) was added to the reaction and the solution was extracted with aqueous sodium bicarbonate. The aqueous phase was acidified with dilute hydrochloric acid and extracted with benzene. The aromatic layer was washed with brine, dried and concentrated to afford, after recrystallisation from methylene chloride, pure acid-ester (12a) (0·96g; 96%), m.p. 95-95·5°, by g.l.c. analysis on the corresponding dimethyl ester (17a).

5-carbomethoxy-2-(p-methoxyphenyl)-cyclohexane-1-carboxylic acid (21a).

Cis-acid-ester (12a) (15g; 0·05mol), in methyl acetate (600ml), was quantitatively hydrogenated over Adam's catalyst (6mg) at room temperature and pressure during 1 hour. Removal of the catalyst and solvent afforded the cis-acid-ester (21a) as a white powder. Recrystallisation from chloroform afforded colourless prisms of pure acid-ester (21a) (14·9g; 98%) m.p. 122-123°, ν max. (KBr) 1735 cm^{-1} (ester C=O) and 1705 cm^{-1} (acid C=O), λ max. 227 nm (13,380), 276 nm (ϵ 1,960) and 283 nm (ϵ 1,700), δ 10·1 (1H,s,COOH), 7·24-6·83 (4H,q of d,J=9,2Hz,aryl H), 3·80 (6H,2 x s,OMe), 3·79 (1H,m,benzylic H) and 2·4-1·6 (8H,m,aliphatic H) (Found: C, 65·5; H, 6·84%; M^+, 292. $C_{16}H_{20}O_5$ requires C, 65.7; H, 6·84%; M^+ 292).

Hydrogenation of an epimeric mixture of 5-carbomethoxy-2-(p-methoxyphenyl)-cyclohex-3-en-1-carboxylic acids (12a) and (12b).

A 1:1 mixture of crystalline, epimeric acid-esters (12a) and (12b) (5g; 17mmol) in methyl acetate (325ml) was hydrogenated over Adam's catalyst (8mg) at room temperature and pressure for 4 days to yield, after the usual work up and recrystallisation from chloroform, a 1:1 mixture of the dihydro acid-esters (21a) and (21b) (3·7g; 73%), m.p. 93-99°, ν max. (KBr) 1735 cm^{-1} (ester C=O) and 1705 cm^{-1} (acid C=O), δ 10·1 (1H,s,COOH), 7·24-6·83 (4H,q of d,J=9,2Hz,aryl H), 3·8 (6H,2 x s,OMe), 3·78 (1H,m,benzylic H) and 2·4-1·6 (8H, m,aliphatic H) (Found: M^+, 292. $C_{16}H_{20}O_5$ requires M^+, 292).

Methyl 1,2,3,4,4a(βH),9a(βH)-hexahydro-7-methoxy-9-oxofluorene-2-carboxylate (5a).

Preparation from the acid-ester (21a).

A suspension of the cis-acid-ester (21a) (14·6g; 0·05mol)in oxalyl chloride (8·3ml; 0·1mol) and anhydrous benzene (200ml) was stirred at room temperature for 2 hours and at 50° for 1 hour, whereupon the resulting solution became homogeneous and no further evolution of hydrogen chloride was detected. The benzene and excess oxalyl chloride were removed at water pump pressure, leaving the acid chloride (23) as a clear oil (νmax. (film) 1789 cm^{-1}(acid chloride C=O) and 1731 cm^{-1} (ester C=O)).

To a stirred solution of the acid chloride (23) (9·3g; 0·03mol) in anhydrous methylene chloride (400ml) at -15°, was added slowly over 2 hours, aluminium trichloride (12g; 0·09mol). The suspension was then allowed to warm to room temperature and stirring was continued for a further 24 hours, whereupon the mixture was poured onto crushed ice and extracted with ethyl acetate. The organic extract was washed successively with aqueous sodium bicarbonate, water and brine, dried and concentrated to afford a brown, polymeric solid (8·4g) which was disolved in ethyl acetate (18ml), filtered and concentrated to afford an orange oil (1·5g). Chromatography of the oil on silica gel eluted with hexane-ethyl acetate (83:17) produced, after the usual work up, the hydrofluorenone (5a) (0·31g; 3·8%) as a yellow oil b.p. 86-87·5° at 0·01mm, shown to be a single epimer by g.l.c. analysis, ν max. (CCl_4) 1740 cm^{-1} (ester C=O) and 1701 cm^{-1} (benzylic cyclopentanone C=O), λ max. 223 nm (ϵ 8,500), 252 nm (ϵ 3,900) and 332 nm (ϵ 1,320), δ 7·42 (1H, d,J=9Hz,aryl-5-H), 7·34 (1H,d,J=2Hz,aryl-8-H), 7·14 (1H,q, J=9,2Hz,aryl-6-H), 3·82 (3H,s,OMe), 3·62 (3H,s,OMe), 3·41 (1H,m,benzylic H) and 2·65-0·95 (8H,m,aliphatic H) (Found: C, 69·56; H, 6·9%, M^+, 274·120. $C_{16}H_{18}O_4$ requires C, 70·07; H, 6·6%, M^+, 274·120).

Since elemental analysis proved unsatisfactory, the corresponding crystalline hydroxy-ester (69) was prepared (see below).

Work up of the aqueous sodium bicarbonate fractions, in the usual manner, afforded , after recrystallisation from chloroform, starting material (21a)

(0·54g), m.p. 121·5-123°. No other products could be satisfactorily identified from either the aqueous or organic phases.

Methyl 1,2,3,4,4a(βH),9a(βH)-hexahydro-7-methoxy-9α-hydroxyfluorene-2-carboxylate (69).

A solution of the keto-ester (5a) (1g; 3·65mmol) in anhydrous methanol (50ml) was stirred at 0° and sodium borohydride (0·31g; 8mmol) was added over 30 minutes. The suspension was then stirred at room temperature for a further hour and then cold water was added, followed by dilute hydrochloric acid. The two phase solution was extracted with ethyl acetate and the organic layer was then washed with brine dried and concentrated to afford a white powder. Recrystallisation from methylene chloride afforded colourless needles of the hydroxy-ester (69) (0·91g; 90·4%), m.p. 121-122°, νmax.(KBr) 1732 cm^{-1} (ester C=O) and 3401 cm^{-1} (alcohol), λmax. 210 nm (ϵ 1,270), 250 nm (ϵ 1,890), 281 nm (ϵ 2,340) and 288 nm (ϵ 1,770), δ 7·24 (1H,d,J=9Hz, aryl-5-H), 7·00 (1H,d,J=2Hz,aryl-8-H), 6·74 (1H,q,J=9,2Hz,aryl-6-H), 5·24 (1H,d,J=5Hz,α-hydroxybenzylic H), 3·82 (3H,s,OMe), 3·60 (3H,s,OMe), 3·22 (1H,m,benzylic H), 3·20 (1H,s,ROH) and 2·6-0·9 (8H,m,aliphatic H) (Found: C, 69·8; H, 7·45%. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·25%).

Treatment of 5-carbomethoxy-2-(p-methoxyphenyl)-cyclohexan-1-oic acid (21a) with polyphosphoric acid - formation of endo-2-(p-methoxyphenyl)-cyclohexan-cis-1,5-dicarboxylic acid anhydride (24).

Powdered acid-ester (21a) (14·6g; 0·05mol) was added over 30 minutes to polyphosphoric acid (prepared as described by Robinson[67] by heating phosphorus pentoxide (150g) and phosphoric acid (150ml) at 100° for 1 hour) and then the mixture was stirred at 60° for 2 hours. The mixture was then poured onto crushed ice and stirred for

30 minutes. Cold, dilute hydrochloric acid was added and stirring was continued for a further 10 minutes, whereupon ethyl acetate (2 x 150ml) was used to extract the aqueous solution. The organic extract was washed successively with aqueous sodium bicarbonate, water and brine, dried and concentrated to afford a brown gum (9·8g). After addition of methylene chloride (17ml) and filtration of the resulting solution, a tan coloured oil was obtained on concentration. Crystallisation from methylene chloride afforded a cream-coloured solid which, on recrystallisation from methylene chloride, afforded colourless needles of the anhydride (24) (0·56g; 4·3%), m.p. 147-148°, ν max. (KBr) 1815,1771 cm^{-1} (glutaric anhydride[27]), λ max. 227 nm (ϵ 10,000), 276 nm (ϵ 2,140) and 283 nm (ϵ 1,780), δ 7·2-6·8 (4H,q, J=9Hz,aryl H), 3·76 (3H,s,OMe), 3·3-2·8 (5H,m,aliphatic H) and 2·2-1·8 (4H,m,aliphatic H) (Found: C, 69·38; H, 6·32%. $C_{15}H_{16}O_4$ requires C, 69·23; H, 6·16%).

The sodium bicarbonate extracts were acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic fraction was washed with brine, dried and concentrated to afford starting material (21a) (4·7g), as a crude white powder. Recrystallisation from chloroform afforded starting material (21a) (3·6g), m.p. 121-122·5°. The remaining material (1·1g) was chromatographed on a preparative, thick layer, silica plate and developed in hexane-ethyl acetate-acetic acid (54-45-1) and afforded, after recrystallisation from chloroform, a further sample of starting material (21a) (0·8g), m.p. 122-123°. No hydrofluorenes were detected.

1,5-dicarbomethoxy-2-(p-methoxyphenyl)-cyclohex-3-enes (17a) and (17b) from the Diels Alder reaction between methyl 5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoate (11) and methyl acrylate.

a) Methyl acrylate as solvent.

A solution of the diene-ester (11) (4·0g; 18·34mmol)

and hydroquinone (2mg) in methyl acrylate (17·4g; 0·2mol) was refluxed under a nitrogen atmosphere for 10 days. The reaction solution was then evaporated to afford a semi-solid mass which recrystallised from methanol to yield pure diene-ester (11) (2·05g), m.p. 126-127° (lit.[30] m.p. 126-127°). The mother liquor was chromatographed on silica gel (150g) and eluted with hexane-chloroform (90:10 - 75:25) to afford more diene-ester (11) (0·85g), m.p. 126-127°, and an epimeric mixture of the diesters (17a) and (17b) (1·35g; 25%), which, by g.l.c. analysis proved to be in a 7:3 ratio in favour of the cis-diester (17a).

b) Benzene as solvent.

A solution composed of the diene-ester (11) (4·0g; 18·34mmol), methyl acrylate (1·74g; 20mmol), hydroquinone (2mg) and anhydrous benzene (60ml) was refluxed for 4 days under a nitrogen atmosphere. The reaction solution was then evaporated to afford an orange, semi-solid mass which was recrystallised from methanol to yield pure diene-ester (11) (3·16g), m.p. 126-127°. The mother liquor was chromatographed as in a) to afford a further sample of the diene-ester (11) (0·38g), m.p. 126-127°, and an epimeric mixture of the diesters (17a) and (17b) (0·56g; 10%) in a 13:7 ratio in favour of the cis-diester (17a).

c) Methylene chloride as solvent with the dienophile activated by aluminium chloride.

A solution of the dienophile, methyl acrylate, (1·75g; 20mmol), hydroquinone (2mg) and methylene chloride (50ml) was stirred at -30° under a nitrogen atmosphere. Resublimed aluminium chloride (5·34g; 40mmol) was added slowly over 1 hour while stirring was continued at -30°. A solution of the diene-ester (11) (4·0g; 18·34mmol) in dry methylene chloride (50ml) was added dropwise and the resulting suspension stirred for a further 2 hours at -30° and then at room temperature overnight. The suspension was

poured onto crushed ice and extracted with chloroform. The organic extract was successively washed with aqueous sodium bicarbonate, water and brine, dried and concentrated to afford a viscous, orange oil which was chromatographed as in a) to yield pure diene-ester (11) (0·7g), m.p. 126-127°, and a mixture of the epimeric diesters (17a) and (17b) (4·5g; 80%), in a 3:2 ratio in favour of the cis-epimer (17a).

d) Methylene chloride as solvent with the diene (11) pre-reacted with aluminium chloride.

A solution of the diene-ester (11) (4·0g; 18·34mmol), hydroquinone (2mg) and methylene chloride (150ml) was stirred at -30° under a nitrogen atmosphere. Resublimed aluminium chloride (4·9g; 37mmol) was slowly added over 1 hour while stirring was continued at -30°. A solution of methyl acrylate (1·74g; 20mmol) in dry methylene chloride (20ml) was added dropwise and the resulting suspension was stirred at -30° for a further 2 hours and then at room temperature overnight. The suspension was worked up as in c) to yield pure diene-ester (11) (1·7g), m.p. 126-127°, and an epimeric mixture of the diesters (17a) and (17b) (2·8g; 45%), in a 13:7 ratio in favour of the cis-epimer (17a).

Cis-1,5-dicarbomethoxy-2-(p-methoxyphenyl)-cyclohex-3-ene (17a).

Excess ethereal diazomethane was added to the acid-ester (12a) (1g; 3·4mmol) and the solution stirred for 30 minutes at room temperature. Removal of the polymer and solvent, followed by column chromatography on silica gel (200g) eluted with hexane-chloroform (85:15), afforded pure diester (17a) (0·98g; 94%), b.p. 105-106° at 0·01mm, ν max. (CCl_4) 1745 cm^{-1} (broad) (ester C=O), λ max. 226 nm (ϵ 20,100), 276 nm (ϵ 4,000) and 283 nm (ϵ 3,700), δ 7·5-6·7 (4H,q of d, J=9,2Hz,aryl H), 5·93 (2H,m,olefinic H), 3·81 (3H,s,OMe), 3·68 (3H,s,OMe), 3·59 (1H,m,benzylic H) and 2·4-1·6 (4H,

m,aliphatic H) (Found: M^+, 304·1302. $C_{17}H_{20}O_5$ requires M^+, 304·1310).

2-(p-methoxyphenyl)-cyclohex-3-en-1,5-dicarboxylic acids (18a) and (18b) from the Diels Alder reaction between 5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoic acid (13) and acrylic acid.

a) Benzene as solent.

A solution of the diene-acid (13) (6·0g; 29·41 mmol), acrylic acid (2·9g; 40mmol), hydroquinone (2mg) and anhydrous benzene (150ml) was refluxed under a nitrogen atmosphere for 14 days. The reaction solution was cooled and a further addition of benzene (350ml) used to dilute the solution which was then washed with water to remove all traces of unreacted dienophile and then with brine, and the resulting solution was left standing at room temperature overnight (winter). The crude solid which formed was filtered off and recrystallised from chloroform to yield an epimeric mixture of the diacids (18a) and (18b) (0·35g). The mother liquor was returned to the benzene fraction which was dried and concentrated to afford a fluffy, yellow solid. This was disolved in ethyl acetate and column chrmatographed on neutral alumina (250g) and eluted with petrol-ethyl acetate-acetic acid (78-20-2) to afford two fractions which were worked up and recrystallised from the appropriate solvents to yield diene-acid (13), m.p. 182-183° and an epimeric mixture of the diacids (18a) and (18b) (0·28g). The total yield of the diacids was (0·63g; 8%), m.p. 128-134°. G.l.c. analysis of the esterified diacid mixture revealed a 1:1 ratio of cis- (18a) and trans-diacids (18b).

b) Acrylic acid as solvent.

A solution of the diene-acid (13) (4·16g; 20·4 mmol) and hydroquinone (1·5mg) in acrylic acid (20ml) was

refluxed under a nitrogen atmosphere for 6 days. High vacuum distillation removed unreacted dienophile and the crude solid residue was chromatographed on neutral alumina (500g) and eluted with the tertiary solution as used in a) to afford after recrystallisation from the appropriate solvents a 1:1 ratio of the diacids (18a) and (18b) (0·1g; 1·8%) and pure diene-acid (13).

5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoyl chloride (14).

To a warm (45°) solution of 5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoic acid (13) (27·5g; 0·135mol) in anhydrous benzene (1500ml) containing pyridine (1ml) was added over 30 minutes thionyl chloride (20g; 0·168mol) in dry benzene (50ml) and the resulting solution was refluxed until the evolution of hydrogen chloride had ceased (about 4 hours). The solution was filtered hot to remove the pyridinium hydrochloride and then evaporated. The resulting yellow solid was disolved in dry ether (50ml) and re-evaporated to remove all traces of unreacted thionyl chloride. Recrystallisation from benzene-ether afforded long, yellow needles of pure acid chloride (14) (28·1g; 93·7%), m.p. 73-74°, νmax. (KBr) 1742 cm^{-1} (acid chloride, highly conjugated C=O), λmax. 283 nm (ϵ 17,500) and 332 nm (ϵ 33,400), δ 7·5-6·8 (4H,q,J=9Hz,aryl H), 7·7-6·8 (3H,m, vinyl H), 6·11 (1H,d,J=14Hz,2-H) and 3·81 (3H,s,OMe) (Found: C, 64·67; H, 4·82%, M^+, 220,222 (3:1 ratio). $C_{12}H_{11}O_2Cl$ requires C, 64·72; H, 4·99%, M^+, 220·5).

2-(p-methoxyphenyl)-cyclohex-3-en-cis-1,5-dicarboxylic acid (18a).

a) From the Diels Alder reaction between acrylyl chloride and 5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoyl chloride (14).

A slurry of acrylyl chloride (18·1g; 0·20mol), freshly prepared from benzoyl chloride and acrylic acid as outlined by Cross[68], hydroquinone (3mg) and the dienoyl chloride (14) (30g; 0·135mol) was heated at 76° for 4 days under a nitrogen atmosphere until no trace of the diene remained (followed most conveniently by ultra-violet spectroscopy). The solution containing the diacid chloride (20) of the desired diacid (18a) was then evaporated to remove all traces of the unreacted dienophile and the resulting orange gum was cooled in an ice bath while aqueous acetone (50ml) was added very slowly to hydrolyse the resulting Diels Alder aduct (20) to the required diacid (18a). After the evolution of hydrogen chloride had ceased, the solution was warmed to 50° and water was added until a white precipitate appeared, whereupon a few drops of acetone were added to redisolve the precipitate, and the resulting solution was then allowed to cool to room temperature slowly to afford white, pyramidal crystals of the diacid (18a). On further cooling in a refrigerator a further batch of crystals appeared. The crystals were recrystallised from chloroform-petrol to afford pure diacid (18a), m.p. 138·5-139·5°.

G.l.c. analysis of the crystals, in the form of their dimethyl ester (17a), revealed that they consisted of only one isomer, while the mother liquor was composed of an epimeric mixture of the diacids (18a) and (18b) in the ratio 87:13 in favour of the former monomer. Recrystallisation of the mother liquor from chloroform-petrol afforded a further sample of the cis-diacid (18a) (3·8g); the total yield of the diacid (18a) m.p. 138·5-139·5°, was 90%, $\nu_{max.}$ (KBr) 1706 cm^{-1} (broad) (acid C=O), $\lambda_{max.}$ 228 nm (ϵ 18,000), 276 nm (ϵ 4,200) and 283 nm (ϵ 3,500), δ 11·4 (2H,broad s,COOH), 7·3-6·8 (4H,q of d,J=9,2Hz,aryl H), 5·96 (2H,m,olefinic H), 3·80 (3H,s,OMe), 3·78 (1H,m,benzylic H) and 2·6-1·9 (4H, m,aliphatic H) (Found: C, 65·5; H, 5·97%. $C_{15}H_{16}O_5$ requires C, 65·21; H, 5·84%).

When the reaction was repeated using acrylyl chloride (1·8g; 20mmol) and dienoyl chloride (14) (3·0g; 13·5mmol) under refluxing conditions in the presence of

hydroquinone (0·5mg), for 2 days , work up as above produced an epimeric mixture of the diacids (18a) and (18b), m.p. 128-134°, (85%), in a 17:3 ratio in favour of the former monomer.

b) From the Diels Alder reaction between acrylyl chloride and 5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoic acid (13).

A solution of the diene-acid (13) (6·0g; 29.41 mmol), hydroquinone (2mg) and acrylyl chloride[68] (50g, 0·575 mol) was refluxed under a nitrogen atmosphere for 4 days and then evaporated under a high vacuum, oil pump to afford a yellow gum which was stirred in dry acetone (10ml) on an ice bath and aqueous acetone added dropwise. The solution was then warmed and water added dropwise until a precipitate appeared. On addition of a few drops of hot acetone the solution resumed its original transparency and was left to crystallise overnight. The resulting white solid was collected and on refrigerating the mother liquor, a further batch of solid was obtained. Recrystallisation from chloroform afforded an epimeric mixture of the diacids (18a) and (18b), m.p. 130-134·5° (6·9g; 85%) in the ratio 3:1 in favour of the former monomer.

Epimerisation of methyl 2-(p-methoxyphenyl)-cyclohex-3-en-cis-1,5-dicarboxylate (17a).

In alkaline media.

a) The diester (17a) (1g; 3·28mmol), disolved in methanol (50ml), was added to a saturated solution of sodium carbonate (50ml) and the resulting solution was refluxed overnight. The solution was extracted with ethyl acetate and the organic phase was then washed with brine, dried and concentrated to afford the diester (17a) (0·94g), g.l.c. analysis of which revealed that epimerisation had not

occurred.

b) The diester (17a) (1g; 3·28mmol), disolved in methanol (50ml), was added to a 0·2M sodium hydroxide solution (50ml) and stirred for 5 minutes at room temperature. On acidification with dilute hydrochloric acid and extraction with ethyl acetate, the organic phase was washed with brine dried and concentrated to leave a crude, white powder. Recrystallisation from chloroform-petrol afforded pure diacid (18a) (0·88g; 97%), m.p. 138·5-139·5° as a single isomer.

c) The diester (17a) (1g; 3·28mmol), disolved in methanol (50ml), was added to 1M sodium hydroxide (50ml) and stirred for 5 minutes at room temperature. On work up as in b), an epimeric mixture of the diacids (18a) and (18b) (0·89g; 97·5%), was obtained in a 2:1 ratio in favour of the former monomer.

d) The diester (17a) (1g; 3·28mmol), disolved in methanol (50ml), was added to 0·2M sodium hydroxide (50ml) and stirred for 15 minutes at 50°. On work up as in b), an epimeric mixture of the diacids (18a) and (18b) (0·85g; 94%), was obtained in a 2:1 ratio in favour of the former monomer.

<u>In acidic media.</u>

a) The diester (17a) (1g; 3·28mmol), in methanol (50ml), was added to 0·2M hydrochloric acid (50ml) and stirred overnight at room temperature. The aqueous solution was extracted with ethyl acetate and the organic phase was then washed with brine, dried and concentrated to afford the cis-diester (17a) as the sole reaction product.

b) The diester (17a) (1g; 3·28mmol), in methanol (50ml), was added to 1M hydrochloric acid (50ml) and stirred overnight at room temperature. On work up as in a), a white powder was obtained. Recrystallisation from chloroform-petrol afforded an epimeric mixture of the diacids (18a)

and (18b) (0·67g; 74%) in a 2:1 ratio in favour of the former monomer.

c) The diester (17a) (1g; 3·28mmol), in methanol (50ml), was added to 0·2M hydrochloric acid (50ml) and stirred at 50° for 3 hours. On work up as in b), an epimeric mixture of the diacids (18a) and (18b) (0·75g; 83%), in a 2:1 ratio in favour of the former monomer, was obtained.

Epimerisation of 2-(p-methoxyphenyl)-cyclohex-3-en-cis-1,5-dicarboxylic acid (18a).

In alkaline media.

a) The diacid (18a) (1g; 3.62mmol), in methanol (50ml), was added to 1M sodium hydroxide (50ml) and stirred at room temperature overnight. The solution was then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford a white powder. Recrystallisation from chloroform-petrol gave pure diacid (18a) (0·94g), m.p. 138-139·5°, as a single isomer.

b) The diacid (18a) (1g; 3·62mmol), in methanol (50ml), was added to 1M sodium hydroxide (50ml) and stirred overnight at 50°. On work up as in a), a 2:1 mixture of the diacids (18a) and (18b), respectively, (0·90g) was obtained.

c) The diacid (18a) (1g; 3·62mmol), in methanol (50ml), was added to 3M sodium hydroxide (50ml) and stirred overnight at room temperature. On work up as in a), a 2:1 mixture of the diacids (18a) and (18b) (0·92g) was obtained in favour of the former monomer.

In acidic media

a) The diacid (18a) (1g; 3·62mmol), in methanol (50ml), was

added to 1M hydrochloric acid (50ml) and the resulting suspension was stirred at room temperature overnight. The aqueous solution was extracted with ethyl acetate and the organic fraction was washed with brine, dried and concentrated to afford, after recrystallisation from chloroform-petrol, pure diacid (18a) (0·94g), m.p. 138·5-139·5°, as a single isomer.

b) The diacid (18a) (1g; 3·62mmol), in methanol (50ml), was added to 1M hydrochloric acid (50ml) and stirred overnight at 50°. On work up as in a), a 2:1 mixture of the diacids (18a) and (18b) (0·89g) was obtained in favour of the former monomer.

c) The diacid (18a) (1g; 3·62mmol), in methanol (50ml), was added to 3M hydrochloric acid (50ml) and stirred overnight at room temperature. On work up as in a), a 2:1 mixture of the diacids (18a) and (18b) (0·93g) was obtained in favour of the former monomer.

2-(p-methoxyphenyl)-cyclohexane-cis-1,5-dicarboxylic acid (22a).

The diacid (19a) (10·0g; 36mmol) was disolved in ethyl acetate (400ml) and quantitatively hydrogenated over Adam's catalyst (4mg) at room temperature and pressure. Removal of the catalyst and solvent afforded almost pure diacid (22a) as a white solid. Recrystallisation from chloroform-petrol gave colourless needles of diacid (22a) (9·91g; 98%), m.p. 156-157°, ν max. (KBr) 1708 cm^{-1}(broad) (acid C=O), λmax. 228 nm (ϵ 17,800), 276 nm (ϵ 4,170) and 283 nm (ϵ 3,900), δ 11·24 (2H,broad s,COOH), 7·3-6·8 (4H,q of d,J=9,2Hz,aryl H), 3·86 (3H,s,OMe), 3·79 (1H,m,benzylic H) and 2·6-1·6 (8H,m,aliphatic H) (Found: C, 64·80; H, 6·60%. $C_{15}H_{18}O_5$ requires C, 64·76; H, 6·48%).

Hydrogenation of an epimeric mixture of 2-(p-methoxyphenyl)-cyclohex-3-en-1,5-dicarboxylic acids (18a) and (18b).

Treatment of a mixture of the epimeric diacids (18a) and (18b) (2·76g; 10mmol) in ethyl acetate (150ml) with Adam's catalyst (3mg), while stirring was carried out under a hydrogen atmosphere at room temperature and pressure for 4 days, afforded on the normal work up and recrystallisation from chloroform, an inseparable mixture of the epimeric diacids (22a) and (22b) (1·81g; 65%), m.p. 137-142°, ν max. (KBr) 1708 cm^{-1} (broad) (acid C=O), δ 11·24 (2H,broad s,COOH), 7·3-6·8 (4H,q of d,J=9,2Hz,aryl H), 3·80 (3H,s,OMe), 3·75 (1H,m,benzylic H) and 2·6-1·6 (8H,m, aliphatic H) (Found: M^+, 278. $C_{15}H_{18}O_5$ requires M^+, 278).

Alternative preparation of endo-2-(p-methoxyphenyl)-cyclohexane-cis-1,5-dicarboxylic acid anhydride (24).

a) The cis-diacid (22a) (5·0g; 18mmol) was disolved in redistilled acetic anhydride (400ml) and the resulting solution was stirred for 4 hours at 60°. The solvent was removed under high vacuum to precipitate the anhydride (24) as a white solid. Recrystallisation from methylene chloride afforded almost quantitative yields of the anhydride (24) (4·61g; 98·5%), m.p. 147-148°, identical in all respects to that prepared from the polyphosphoric acid treatment of the acid-ester (21a).

b) A 1:1 mixture of the epimeric diacids (22a) and (22b) (1g; 3·6mmol) in redistilled acetic anhydride (200ml) was stirred at 75° for 24 hours. The solvent was removed under high vacuum to leave a brown oil which refused to crystallise. The oil was refrigerated for 1 week but still refused to crystallise. Thin layer chromatographic analysis revealed the presende of at least three components of very similar R.f. values, one of which corresponded to the endo-anhydride (24). Spectroscopic analysis of the oil revealed the

presence of the anhydride (24) ν max. 1316, 1770 cm^{-1} (glutaric anhydride), δ max. 3·76 (3H,s,OMe). Aqueous hydrolysis of the oil using hot water for 5 hours produced a 1:1 epimeric mixture of the diacids (22a) and (22b) as the sole products.

1,2,3,4,4a(βH),9a(βH)-hexahydro-7-methoxy-9-oxofluorene-2-carboxylic acid (29a).

The endo-anhydride (24) (10g; 38mmol) was disolved in anhydrous, redistilled methylene chloride (600ml) and cooled to -20° in an isopropanol-drikold bath. 4 equivalents of triply sublimed aluminium chloride (20g; 0·15mol) was added very slowly over 2 hours while the suspension was vigorously stirred at -20° and stirring was continued for a further 2 hours when the suspension was allowed to warm to room temperature. The cyclisation was monitored by ultra-violet spectroscopy and after a further 4 hours the mixture was poured onto crushed ice and extracted with chloroform. The organic phase was washed with water and brine, dried and concentrated to afford a white powder, a sample of which was esterified and subjected to g.l.c. analysis. This revealed the presence of 92% of the desired keto-acid (29a) and 8% of the cis-diacid (22a).

It proved impossible to isolate the keto-acid (29a) from the diacid (22a) by crystallisation. The three separation methods which proved most fruitful were:

a) Column chromatography on silica gel (200g) of the crude reaction mixture (5g) gave, on elution with hexane-ethyl acetate-acetic acid (80-18-2 : 49-49-2), keto-acid (29a) which, on recrystallisation from ethyl acetate-hexane, afforded pure keto-acid (29a) (4·27g; 85% based on the anhydride (24)), m.p. 182-183°.

b) Recyclisation of the reaction mixture by disolving the mixture of the keto-acid (29a) and the diacid (22a) in

acetic anhydride(300ml) and heating the resultant solution at 60° for 4 hours. The solvent was removed under high vacuum and the resulting white precipitate was disolved in anhydrous methylene chloride (300ml) and cooled to -20°. Triply sublimed aluminium chloride (7g) was slowly added over 1·5 hours and the resulting suspension was then allowed to warm to room temperature. On work up as above, g.l.c. analysis revealed 98% of the keto-acid (29a) and 2% of the diacid (22a). Recrystallisation from ethyl acetate-hexane afforded pure keto-acid (29a) (4·82g; 96% based on the endo-anhydride (24)), m.p. 182-183°.

c)Reduction of the crude mixture followed by oxidation.

An intimate mixture of the acids (22a) and (29a) was stirred in anhydrous methanol (5g/150ml) on an ice bath. Freshly prepared sodium borohydride[65] (2g) was slowly added over 30 minutes and the resulting suspension was then allowed to warm to room temperature while stirring was continued for a further 2 hours. The reaction mixture was then poured onto crushed ice, acidified with cold, dilute hydrochloric acid, extracted with ethyl acetate, with the organic phase then being washed with brine, dried and concentrated to afford a crude, white solid. Recrystallisation from methylene chloride afforded pure hydroxy-acid (37a) as the sole product (4·2g; 83% based on the anhydride (24)), m.p. 177-178°, leaving the diacid (22a) in the mother liquor.

Oxidation of the alcohol (37a) (2·5g; 9mmol) in acetone (20ml) with 5M Jones reagent, followed by extraction with ethyl acetate, washing of the organic phase with water and brine, drying and concentration, produced a fine, white powder. Recrystallisation from ethyl acetate-hexane afforded pure keto-acid (29a) (2·2g; 74% based on the endo-anhydride (24)), m.p. 182-183°, νmax. (KBr) 1698 cm^{-1}(broad) (overlapping acid C=O and indan-1-one C=O), λmax. 224 nm (ϵ 8,500), 249 nm (ϵ 4,500) and 323 nm (ϵ 1,700), δ 10·1 (1H,s,COOH), 7·45 (1H,d,J=9Hz,aryl-5-H), 7·35 (1H,d.J=2Hz,aryl-8-H), 7·15 (1H,q,J=9,2Hz,aryl-6-H), 3·81 (3H,s,OMe), 3·42 (1H,m,

benzylic H) and 2·6-1·0 (8H,m,aliphatic H) (Found: C, 69·45; H, 6·07%; M^+, 260. $C_{15}H_{16}O_4$ requires C, 69·23; H, 6·16%; M^+, 260).

Alternative preparation of methyl 1,2,3,4,4a(βH),9a(βH)-hexahydro-7-methoxy-9-oxofluorene-2-carboxylate (5a).

A solution of excess diazomethane was added to the keto-acid (29a) (5·0g; 17·23mmol) and the resulting solution was stirred at room temperature for 30 minutes. Removal of the solvent and the polymer, followed by high vacuum distillation, afforded the keto-ester (5a) (3·55g; 67·5%), b.p. 86-87·5° (0·01mm) as a yellow, viscous oil identical in all respects to that produced by the Friedel Crafts acylation of the acid chloride (23).

Methyl (1,2,3,4,4a(βH),9a-hexahydro-2-carbomethoxy-7-methoxy-9-oxofluorene-9aβ)-acetates (39a) and (39b).

A solution of the keto-ester (5a) (4·7g; 17mmol) in anhydrous t-butanol (20ml) was added to a potassium-t-butoxide/t-butanol solution (prepared from potassium (0·782g; 0·02 g-atoms) and t-butanol (50ml)) dropwise over 30 minutes while stirred under a nitrogen atmosphere at 45°. Stirring was continued for a further 2 hours at 45° and then the reaction was allowed to cool to 30°, and a solution of methyl bromoacetate (1·04g; 6·8mmol) in t-butanol (20ml) was added dropwise to the above solution at 30°. The resulting solution turned cloudy due to the formation of potassium bromide, which was precipitated from the reaction medium. The solution was stirred for a further 6 hours, then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford a tan coloured oil which contained trace amounts of acidic material. The oil was stirred in the presence of a solution of excess diazomethane for 30 minutes and after the removal of the solvent and

polymer, was chromatographed on silica gel (200g) and eluted with ethyl acetate-hexane (15:85). Two fractions were separated: an epimeric mixture of the starting keto-ester (5a) and its monomer (5b) (1.2g) and an epimeric mixture of the keto-diesters (39a) and (39b) (3·06g; 52%). The remaining material remained at the head of the column and proved to be polymeric.

G.l.c. analysis of the keto-esters (5a) and (5b) revealed that both were present in the mixture in a 1:1 ratio, while analysis of of the mixture of keto-diesters (39a) and (39b) revealed a ratio of 3:2 in favour of the less polar monomer, the stereochemistry of which was not determined. Analysis of the epimeric mixture of the keto-diesters (39a) and (39b) gave b.p. 154-156° (0·02mm), ν max. (CCl_4) 1700 cm^{-1} (indanone C=O) and 1740-1750 cm^{-1} (broad) (ester C=O), λ max. 225 nm (ϵ 9,200), 251 nm (ϵ 3,930) and 324 nm (ϵ 1,660), δ (CCl_4) 7·40-6·98 (3H,m,aryl H), 3·82 (3H,s,OMe), 3·66 (3H,s,OMe), 3·64 (3H,s,OMe), 3·49 (1H, t,benzylic H), 2·15 (2H,s,-$\underline{CH_2}$COOMe) and 2·8-1·2 (7H,m, aliphatic H) (Found: C, 65·89; H, 6·46%; M^+, 346. $C_{19}H_{22}O_6$ requires C, 65·90; H, 6·36%; M^+, 346).

G.l.c. analysis of the keto-esters (5a) and (5b) and the keto-diesters (39a) and (39b).

Pure keto-ester (5a) (1g; 3·6mmol) was stirred in a potassium-t-butoxide/t-butanol solution (prepared from potassium (0·06g; 0·004 g-atoms) and t-butanol (50ml)) overnight at 45° under a nitrogen atmosphere. On the usual work up, and esterification with excess diazomethane, an epimeric mixture of the keto-esters (5a) and (5b) was obtained in a 1:1 ratio. This mixture was chromatographed on silica gel (400g) and eluted with hexane-ethyl acetate (86:14). The two fractions obtained were worked up in the usual manner to provide pure keto-ester (5a) (0·39g) and pure keto-ester (5b) (0·41g). Both epimers had almost identical spectroscopic properties, the only difference being that

while the keto-ester (5a) had an indanone carbonyl absorption of 1701 cm^{-1}, its epimer (5b) had an absorption of 1699 cm^{-1}.

Treatment of the keto-ester (5b) (0·29g) with a potassium-t-butoxide/t-butanol solution, as for the keto-ester (5a), revealed on a similar work up, a 1:1 mixture of the epimeric keto-esters (5a) and (5b).

Column chromatography of the epimeric mixture of the keto-diesters (39a) and (39b), prepared from the keto-ester (5a), on silica gel (500g) eluted with hexane-ethyl acetate (84:16) produced two fractions: the first fraction coming of the column was assigned the name of being the less polar monomer (1·73g) and its more polar, epimeric keto-diester (1·09g).

Each monomer (0·5g; 1·44mmol) was disolved in similar potassium-t-butoxide/t-butanol solutions (prepared from potassium (0·05g; 0·0015g-atoms) and t-butanol (40ml)) and stirred at 35° for 4 hours. On the usual work up, g.l.c. analysis of each reaction revealed that each pure epimer had epimerised to afford an epimeric mixture of the keto-diesters (39a) and (39b) in a 3:2 ratio in favour of the less polar monomer.

Methyl (1,2,3,4,4a(βH),9a-hexahydro-2-carbomethoxy-7-methoxy-9α-hydroxyfluorene-9aβ)-acetates (49a) and (49b).

A 3:2 mixture of the keto-diesters (39a) and (39b) (3·40g; 9·82mmol) was disolved in anhydrous methanol (100ml) and stirred in an ice bath. Freshly prepared sodium borohydride[65] (0·76g; 20mmol) was slowly added over 30 minutes and stirring was continued for a further 30 minutes at 0°. The suspension was allowed to warm to room temperature and stirred for a further hour whereupon the suspension was poured onto crushed ice and acidified with dilute hydrochloric acid. The aqueous solution was extracted with ethyl acetate and the organic phase was washed with brine, dried and concentrated to afford an orange oil. High vacuum distillation produced an epimeric mixture of the hydroxy-

diesters (49a) and (49b) (1·9g; 55·6%), b.p. 174-177° (0·02mm), ν max. (film) 1735 cm^{-1} (broad) (ester C=O) and 3485 cm^{-1} (ROH), λ max. 222 nm (ϵ 15,400), 250 nm (ϵ 1,940) and 325 nm (ϵ 650), δ 7·23 (1H,d,J=9Hz,aryl-5-H), 7·00 (1H, d,J=2Hz,aryl-8-H), 6·74 (1H,q,J=9,2Hz,aryl-6-H), 5·18 (1H, broad s,α-hydroxybenzylic H), 3.80 (3H,s,OMe), 3·63 (3H,s,OMe), 3·51 (3H,s,OMe), 3·03 (1H,m,benzylic H), 2·97 (1H,s,ROH) and 2.6-1·1 (9H,m,aliphatic H) (Found: M^+, 348. $C_{19}H_{24}O_6$ requires M^+, 348).

Elemental analysis proved unsatisfactory, and, in an attempt at preparing the corresponding acetate, the olefin (52) was produced.

(1,2,3,9a-tetrahydro-2-carboxy-7-methoxyfluorene-9a)-acetic acid anhydride (52).

A mixture of the hydroxy-diesters (49a) and (49b) (1g; 2·87mmol) was disolved in acetic anhydride (40ml) containing a crystal of p-toluenesulphonic acid, and the resulting solution was stirred overnight at 40° under a nitrogen atmosphere. On removal of the solvent under high vacuum, a crude orange oil was formed. This oil was disolved in methylene chloride, washed with water and brine, dried and concentrated to leave a crude, orange solid. Repeated recrystallisations from methylene chloride-hexane afforded pure, colourless crystals of the olefinic anhydride (52) (0·24g; 29·5%), m.p.164-166°, ν max. (Nujol) 1748,1839 cm^{-1} (anhydride), λmax. 282 nm (ϵ 1,550) and 234 nm (ϵ 4,600), δ (D_3CCOCD_3) 7·64-6·75 (3H,m,aryl H), 6·42 (1H,m,olefinic H), 3·81 (3H,s,OMe), 3·43 (2H,broadish s,benzylic H), 2·76 (2H,broadish s,-$\underline{CH_2}$COOCO-) and 2.4-1·4 (5H,m,aliphatic H) (Found: C, 71·56; H, 5·63%; M^+, 284. $C_{17}H_{16}O_4$ requires C, 71·83; H, 5·63%; M^+, 284).

Methyl (1,2,3,4,4a(βH),9a-hexahydro-2-carbomethoxy-7-methoxyfluorene-9aβ)-acetates (53a) and (53b).

An epimeric mixture of the hydroxy-diesters (49a) and (49b) (3·0g; 8·62mmol), redistilled methyl acetate (200ml) 60% perchloric acid (4drops) and Adam's catalyst (55mg) was stirred for 24 hours under a hydrogen atmosphere at room temperature and pressure. The suspension was then filtered, washed with water and brine, dried and concentrated to afford the diesters (53a) and (53b) as an epimeric mixture of yellow oils (2·77g; 97%). Chromatography of the oil (1·01g) on silica gel (400g) and eluted with hexane-ethyl acetate (95:5 - 80:20) afforded the two epimers as greenish oils of identical spectroscopic properties, b.p. 165-166·5° (0·025mm), ν max. (CCl_4) 1730 cm^{-1} (broad) (ester C=O), λmax. 223 nm (ϵ 7,300), 251 nm (ϵ 2,830) and 324 nm (ϵ 1,110), δ (CCl_4) 7·23 (1H,d,J=9Hz,aryl-5-H), 7·03 (1H,d, J=2Hz,aryl-8-H), 6·81 (1H,q,J=9,2Hz,aryl-6-H), 3·80 (3H,s, OMe), 3·61 (3H,s,OMe), 3·50 (3H,s,OMe) and 3·4-1·0 (12H,m, aliphatic H) (Found for an epimeric mixture: M^+, 332·16237. $C_{19}H_{24}O_5$ requires M^+, 332·16236).

The stereochemistry of each monomer was not determined. The more polar epimer (100mg) was stirred in methanolic sodium methoxide (prepared from 2 equivalents of solid sodium methoxide (0·6mmol) disolved in anhydrous methanol (30ml)) at room temperature for 30 minutes, acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford a green oil. G.l.c. analysis of this oil revealed its composition to be a 2:1 ratio of the diesters (53a) and (53b) in favour of the less polar monomer.

The less polar monomer (100mg; 0·30mmol) was reacted as above with a methanolic sodium methoxide solution prepared from sodium (0·018g ; 0·7 mmol) in methanol (25ml) solution. G.l.c. analysis of the resulting mixture of epimeric diesters (53a) and (53b) revealed a 2:1 ratio in favour of the less polar monomer as before.

Since an accurate elemental analysis proved abortive, the corresponding acid derivative (61) was prepared (see below).

Methyl (1,2,3,4,4a(βH),9a-hexahydro-2-carboxy-7-methoxyfluorene-9aβ)-acetate (61).

a) An epimeric mixture of the diesters (53a) and (53b) (1·0g; 3·01mmol) was disolved in a solution composed of methanol (30ml), water (5ml) and sodium hydroxide (0·13g; 3·1mmol) and stirred overnight at room temperature under a nitrogen atmosphere. The reaction solution was extracted with ether, acidified and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford a cream-coloured powder (0·89g). The solid was chromatographed on a preparative plate and developed in petrol (60-80)-ethyl acetate-acetic acid (64-35-1). on work up and recrystallisation from methylene chloride-hexane, the acid-ester (61) (0·15g; 16%), m.p. 165-167°, was obtained as an epimeric mixture in the ratio 2:1, as disclosed by g.l.c. analysis on the diesters (53a) and (53b); reformed from the acid-ester (61) on treatment with excess diazomethane. The individual epimers were not separated from the acid-ester (61) which gave the following data: ν max. (Nujol) 1714 cm^{-1} (acid C=O) and 1745 cm^{-1} (ester C=O), λmax. 220 nm (ϵ 13,250), 283 nm (ϵ 4,150), δ 10·35 (1H,s, COOH), 7·28-6·84 (3H,m,aryl H), 3·96 (3H,s,OMe), 3·38 (2H, broadish s,9-benzylic H), 3·94 (1H,m,4a-benzylic H) and 2·4-1·3 (7H,m,aliphatic H) (Found: C, 67·69; H, 6·78%; M^+, 318. $C_{18}H_{22}O_5$ requires C, 67·92; H, 6·91%; M^+, 318).

b) The keto-acid (29a) (2·64g; 10mmol) was disolved in dry t-butanol (50ml) and a solution of potassium-t-butoxide/t-butanol (prepared from potassium (0·98g; 0·025g-atoms) and anhydrous t-butanol (50ml)) was added dropwise while the resulting solution was stirred under a nitrogen atmosphere. The resulting dark-red solution was stirred for a further 5 hours at 55° and then cooled to 30° whereupon a solution of methyl bromoacetate in t-butanol (3·83g; 0.025 mol/25ml) was added dropwise over 30 minutes, while stirring was continued at 30°and then at 45° overnight. The suspension was then acidified with dilute hydrochloric acid

and extracted with ethyl acetate. The organic fraction was washed with brine, dried and concentrated to afford an orange gum. Without any further purification, the gum was disolved in a suspension of methyl acetate (200ml), 60% perchloric acid (4 drops) and Adam's catalyst (100mg). The resulting suspension was stirred under a hydrogen atmosphere at room temperature and pressure for 4 days, filtered and washed with water and brine. On drying and concentration of the solution, a brown gum remained. Column chromatography on neutral alumina (300g) eluted with hexane-ethyl acetate-acetic acid (90-9-1 : 75-24-1) isolated the acid-ester (61). Recrystallisation from methylene chloride-hexane afforded colourless crystals of the acid-ester (61) (1·08g; 34%), m.p. 165-167°. G.l.c. analysis of the crystals revealed that they were composed of the same 2:1 epimeric mixture as those produced in a), despite originating from a single isomeric compound (29a). The spectroscopic properties were also identical with the acid-ester prepared in a).

Attempted Dieckmann cyclisation of a mixture of epimeric keto-diesters (39a) and (39b).

All reactions were performed under a nitrogen atmosphere.

a) Potassium-t-butoxide as base and t-butanol as solvent.[69,70]

An epimeric mixture of the keto-diesters (39a) and (39b) (5·0g; 14·4mmol) was refluxed in a potassium-t-butoxide/t-butanol solution (prepared from potassium (0.6g; 0·015g-atoms) and t-butanol (100ml)) overnight. The solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford a brown gum. Chromatography of the gum on silica gel (200g) eluted with hexane-ethyl acetate (85:15) afforded, as the only isolable products, an epimeric mixture of the keto-diesters (39a) and (39b)

(0·64g); the remaining material remaining at the head of the column.

b) Sodium methoxide as base and benzene as solvent.[30,71,72]

A mixture of the epimeric keto-diesters (39a) and (39b) (3·46g; 10mmol) was disolved in anhydrous benzene (100ml) and added dropwise to freshly prepared, methanol-free, powdered sodium methoxide (prepared from sodium (0·58g; 0·025g-atoms) and anhydrous methanol (50ml)) in dry benzene (40ml). The resulting suspension was refluxed overnight, and on the work up employed in a) yielded an epimeric mixture of the keto-diesters (39a) and (39b) (0·63g) as the sole isolable product.

c) Potassium-t-butoxide as base and benzene as solvent.[73,74]

An epimeric mixture of the keto-diesters (39a) and (39b) (2.0g; 5·78mmol) was disolved in dry benzene (75ml) and added dropwise to a stirred suspension of benzene (25ml) and resublimed (220° 0.1mm) potassium-t-butoxide (1·35g; 0·012mol) and refluxed overnight. On work up as before, the only isolable product was an epimeric mixture of the keto-diesters (39a) and (39b) (0·35g).

d) Sodium methoxide as base and methanol as solvent.

An epimeric mixture of the keto-diesters (39a) and (39b) (3·45g; 10mmol) was disolved in anhydrous methanol (55ml) and added dropwise to a stirred sodium methoxide/methanol solution (prepared from sodium (0·58g; 0·025g-atoms) and dry methanol (50ml)) and the resulting solution was refluxed overnight. On work up as before, an epimeric mixture of the keto-diesters (39a) and (39b) was the sole isolable product.

e) Sodium hydride as base and toluene as solvent.[75]

An epimeric mixture of the keto-diesters (39a) and (39b) (2·16g; 6·24mmol) in dry toluene (75ml) was added

dropwise to a stirred suspension of sodium hydride dispersion (10mmol) in dry toluene (20ml) and refluxed overnight. On the usual work up, only an epimeric mixture of the keto-diesters (39a) and (39b) (0.4g) was isolated.

f) Potassium hydride as base and toluene as solvent.[75]

An epimeric mixture of the keto-diesters (39a) and (39b) (3·3g; 9·53mmol) in dry toluene (80ml) was added dropwise to a stirred suspension of potassium hydride dispersion (12mmol) in anhydrous toluene (30ml) and refluxed overnight. On the usual work up, only an epimeric mixture of the keto-diesters (39a) and (39b) was obtained (0·19g)

Attempted Dieckmann cyclisation of an epimeric mixture of the hydroxy-diesters (49a) and (49b).

All reactions were performed under a nitrogen atmosphere, and a white precipitate was produced in the reaction vessels. The solid was filtered, acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford an epimeric mixture of the hydroxy-diesters (49a) and (49b).

a) Potassium-t-butoxide as base and t-butanol as solvent.[69,70]

A mixture of the epimeric hydroxy-diesters (49a) and (49b) (2·0g; 5·74mmol) was refluxed in a potassium-t-butoxide/t-butanol solution (prepared from potassium (0·25g; 0·006g-atoms) and t-butanol (50ml)) overnight. The solution was then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford a tan coloured oil. Column chromatography of the oil on silica gel (250g) eluted with hexane-ethyl acetate (75:25) gave, as the sole isolable product, an epimeric mixture of the hydroxy-

diesters (49a) and (49b) (1·34g). The remaining material remained at the head of the column and proved to be polymeric by mass spectrometry.

b) Sodium methoxide as base and benzene as solvent.[30,71,72]

An epimeric mixture of the hydroxy-diesters (49a) and (49b) (0·97g; 2·78mmol) was disolved in anhydrous benzene (125ml) and added dropwise to freshly prepared, powdered sodium methoxide (procured from sodium (0·07g; 0.003 g-atoms) and the resulting suspension was refluxed overnight. On work up as in a), the only isolable material was an epimeric mixture of the hydroxy-diesters (49a) and (49b) (0·84g).

c) Sodium methoxide as base and methanol as solvent.

An epimeric mixture of the hydroxy-diesters (49a) and (49b) (1·14g; 3·28mmol) was disolved in dry methanol (20ml) and added dropwise to a stirred solution of methanolic sodium methoxide (prepared from sodium (0·08g; 0·0035g-atoms) and anhydrous methanol (10ml)) and refluxed overnight. On work up as before, an epimeric mixture of the hydroxy-diesters (49a) and (49b) (0·91g) was the only isolable product.

d) Potassium-t-butoxide as base and benzene as solvent.[73,74]

An epimeric mixture of the hydroxy-diesters (49a) and (49b) (2·03g; 5·83mmol) was disolved in anhydrous benzene (170ml) and added dropwise to a stirred solution of benzene (10ml) and resublimed (220° 0·1mm) potassium-t-butoxide (0·69g; 6mmol) and refluxed overnight. On the usual work up an epimeric mixture of the hydroxy-diesters (49a) and (49b) was the only isolable product (1·82g).

e) Sodium hydride as base and toluene as solvent.[75]

An epimeric mixture of the hydroxy-diesters (49a)

and (49b) (0·64g; 1·84mmol) in dry toluene (80ml) was added dropwise to a stirred suspension of sodium hydride dispersion (3mmol) in anhydrous toluene (5ml) and the resulting solution was refluxed overnight. On the usual work up, an epimeric mixture of the hydroxy-diesters was the only isolated product (0·1g).

f) Potassium hydride as base and toluene as solvent.[75]

An epimeric mixture of the hydroxy-diesters (49a) and (49b) (3·19g; 9·16mmol) in dry toluene (270ml) was added dropwise to a stirred suspension of potassium hydride dispersion (10mmol) in anhydrous toluene (15ml) and refluxed overnight. On work up as before, an epimeric mixture of the hydroxy-diesters (49a) and (49b) (2·39g) was the only isolable product.

Attempted Dieckmann cyclisation of an epimeric mixture of the diesters (53a) and (53b).

All reactions were carried out under a nitrogen atmosphere.

a) Potassium-t-butoxide as base and t-butanol as solvent.[69,70]

An epimeric mixture of the diesters (53a) and (53b) (2·01g; 6·02mmol) was disolved in anhydrous t-butanol (30ml) and the resulting solution was added dropwise to a potassium-t-butoxide/t-butanol solution (prepared from potassium (0·24g; 0·006g-atoms) and t-butanol (50ml)) and the resulting solution was refluxed overnight. The solution was then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford a brown gum. This gum was chromatographed on silica gel (200g) and eluted with hexane-ethyl acetate (85:15) to afford an epimeric mixture of the diesters (53a) and (53b) (0·19g). The remaining material

was polymeric (by mass spectrometry) and remained at the head of the column.

b) Sodium methoxide as base and benzene as solvent.[30,71,72]

An epimeric mixture of the diesters (53a) and (53b) (2·46g; 7·5mmol) was disolved in anhydrous benzene (100ml) and the resulting solution was added dropwise to a methanol-free suspension of sodium methoxide (prepared from sodium (0·18g; 0·008g-atoms)) in dry benzene (100ml) and the resulting suspension was refluxed overnight. On the work up employed in a), an epimeric mixture of the diesters (53a) and (53b) (0·23g) was the sole isolable product.

c) Sodium methoxide as base and methanol as solvent.

An epimeric mixture of the diesters (53a) and (53b) (1·87g; 5·03mmol) was disolved in anhydrous methanol (50ml) and added dropwise to a stirred solution of sodium methoxide/methanol (prepared from sodium (0·14g; 0·006g-atoms) and anhydrous methanol (50ml)) and the resulting solution was refluxed overnight. On the usual work up, an epimeric mixture of the diesters (53a) and (53b) (0·14g) was the only isolable product.

d) Potassium-t-butoxide as base and benzene as solvent.[73,74]

An epimeric mixture of the diesters (53a) and (53b) (3·04g; 9·16mmol) in anhydrous benzene (100ml) was added dropwise to a stirred suspension of dry benzene (30ml) and resublimed potassium-t-butoxide (1·28g; 10mmol) and the resulting suspension was refluxed overnight. On the usual work up, an epimeric mixture of the diesters (53a) and (53b) (0·65g) was the only isolable product.

e) Sodium hydride as base and toluene as solvent.[75]

An epimeric mixture of the diesters (53a) and

(53b) (2·45g; 7·37mmol) in dry toluene (100ml) was added dropwise to a stirred suspension of sodium hydride dispersion (12mmol) in anhydrous toluene (40ml) and the resulting suspension was refluxed overnight. On the usual work up, an epimeric mixture of the diesters (53a) and (53b) (0·38g) was the sole isolable product.

f) Potassium hydride as base and toluene as solvent.[75]

An epimeric mixture of the diesters (53a) and (53b) (1·73g; 5·21mmol) in anhydrous toluene (90ml) was added dropwise to a stirred suspension of potassium hydride dispersion (6mmol) in dry toluene (45ml) and the resulting suspension was refluxed overnight. On the usual work up, an epimeric mixture of the diesters (53a) and (53b) (0·15g) was the sole isolable product.

Attempted Dieckmann cyclisation of the pure diesters (53a) and (53b).

The configuration of the less polar epimer and the more polar epimeric diesters (53a) and (53b) were unassigned.

a) Reaction with the less polar epimer.

G.l.c. pure less polar epimeric diester (4·0g; 12mmol) was disolved in anhydrous benzene (100ml) and the resulting solution was added dropwise to a stirred suspension of methanol-free sodium methoxide (15mmol) in anhydrous benzene (70ml) and the resulting suspension was refluxed overnight. On work up as before, the only isolable product was an epimeric mixture of the diesters (53a) and (53b) in a 3:2 ratio in favour of the less polar epimer.

Reactions a)-f) were repeated as for the epimeric mixture, but in all cases the Dieckmann cyclisation failed.

b) Reaction with the more polar epimer.

G.l.c. pure more polar epimeric diester (3·76g; 11·5mmol) was added to methanol-free sodium methoxide (15mmol) in anhydrous benzene (100ml) and the resulting suspension was refluxed overnight. On the usual work up, an epimeric mixture of the diesters (53a) and (53b) (0·26g) was the only isolable product.

1,2,3,4,4a(βH),9a(βH)-hexahydro-7-methoxy-9α-hydroxyfluorene-2-carboxylic acid (37a).

a) Preparation from the keto-acid (29a) by sodium borohydride reduction.

The keto-acid (29a) (2·60g; 0.01mol) was disolved in anhydrous methanol (100ml) and stirred in an ice bath. Freshly prepared sodium borohydride[65] (0·75g; 0·02mol) was added over 30 minutes and the reaction was then allowed to warm to room temperature, whereupon stirring was continued for a further 2 hours. The suspension was poured onto crushed ice and extracted with ethyl acetate, subsequent to the acidification of the ice solution with dilute hydrochloric acid. The organic phase was washed with brine, dried and concentrated to afford a white powder. Recrystallisation from methylene chloride gave pure alcohol (37a) (2·51g; 96%) as long, colourless needles, m.p. 177-178°.

b) Preparation from the keto-acid (29a) by Meerwein-Ponndorf reduction.[76]

The keto-acid (29a) (2·60g; 0·01mol) was disolved in isopropanol (100ml) with freshly prepared aluminium isopropoxide[77] (5·0g; 0·024mol) and refluxed for 6 hours with periodic removal of distillate and replenishment with isopropanol until 2,4-dinitrophenylhydrazine detection of acetone gave a negative result. The solution was then cooled and cold, dilute hydrochloric acid was added and the

resulting aqueous solution was extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford a white solid. Recrystallisation from methylene chloride gave pure hydroxy-acid (37a) (2·07g; 79%), m.p. 177-178°, ν max. (KBr) 1709 cm^{-1} (acid C=O) and 3420 cm^{-1} (ROH), max. 222 nm (ϵ 6,940), 251 nm (ϵ 2,400) and 322 nm (ϵ 1,070), δ 10·94 (1H,s,COOH), 7·22 (1H,d,J=9Hz, aryl-5-H), 7·01 (1H,d,J=2Hz,aryl-8-H), 6·76 (1H,q,J=9,2Hz, aryl-6-H), 5·24 (1H,d,J=5Hz,α-hydroxybenzylic H), 3·82 (3H,s,OMe), 3·21 (1H,m,benzylic H), 3·20 (1H,s,ROH) and 2·9-1·0 (8H,m,aliphatic H) (Found: C, 68·9; H, 7·00%; M^+, 262. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·93%; M^+, 262).

1,2,3,4,4a(βH),9a(βH)-hexahydro-7-methoxyfluorene-2-carboxylic acid (71).

a) Preparation from the keto-acid (29a) by Clemmenson reduction.

The procedure employed was that devised by Wiegrebe[78]. The keto-acid (29a) (2·60g; 0.01mol) was refluxed in 12% aqueous hydrochloric acid (100ml) and amalgamated zinc (7g) (prepared from zinc wool (6g), concentrated hydrochloric acid (0·4ml), mercuric chloride (0·6g) and water (15ml)) for 6 hours. The mixture was cooled and extracted with chloroform (2 x 100ml). The organic extract was washed with brine, dried and concentrated to afford a reddish gum, which was disolved in chloroform (2ml) and refrigerated overnight to produca a cream-coloured solid. On recrystallisation from chloroform-petrol, crude acid (71) (0·64g; 26%), m.p. 158-170° was obtained. Repeated recrystallisations did not decrease the melting point range.

b) Preparation from the keto-acid (29a) by Wolff-Kishner reduction.

The procedure employed was that developed by Baker and Goudie[30]. The keto-acid (29a) (2·60g; 0·01mol) was disolved in a solution composed of ethylene glycol (90ml), hydrazine hydrate (10ml) and potassium hydroxide (1g) and heated at 150° overnight, under a nitrogen atmosphere. The solution was cooled, diluted with water (100ml), acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water and brine, dried and concentrated to yield a brown oil. This oil was chromatographed on neutral alumina (100g) and eluted with hexane-ethyl acetate-acetic acid (83·5-15-1·5) to afford, on the usual work up and recrystallisation from chloroform-petrol, crude acid (71) (0·22g; 9%), m.p. 163-172°. Repeated recrystallisations did not decrease the melting point range.

c) Preparation from the keto-acid (29a) by catalytic hydrogenolysis.

A suspension of the keto-acid (29a) (2·60g; 0·01mol) ethyl acetate (400ml), 60% perchloric acid (4 drops) and Adam's catalyst (60mg) was stirred under a hydrogen atmosphere at room temperature and pressure for 48 hours. The solution was filtered, washed with water and brine, dried and concentrated to leave a white powder. Recrystallisation from chloroform afforded pure acid (71) (1·98g; 80%), m.p. 170-171°.

d) Preparation from the hydroxy-acid (37a) by catalytic hydrogenolysis.

A suspension of the hydroxy-acid (37a) (2·62g; 0·01mol), ethyl acetate (400ml), 60% perchloric acid (4 drops) and Adam's catalyst (60mg) was stirred under a hydrogen atmosphere at room temperature and pressure for 1 hour. The solution was filtered, washed with water and brine, dried and concentrated to afford crystalline acid (71). Recrystallisation from chloroform gave pure, colourless crystals of the acid (71) (2·41g; 98%), m.p. 170-

171°, νmax. (KBr) 1691 cm^{-1} (acid C=O), λmax. 223 nm (ϵ 5,900), 282 nm (ϵ 2,300) and 289 nm (ϵ 2,150), δ 10·01 (1H,s,COOH), 7·21 (1H,d,J=9Hz,aryl-5-H), 6·84 (1H,d,J=2Hz, aryl-8-H), 6·58 (1H,q,J=9,2Hz,aryl-6-H), 3·78 (3H,s,OMe) and 3·4-1·0 (11H,m,aliphatic H) (Found: C, 73·34; H, 7·36%; M^+, 246. $C_{15}H_{18}O_3$ requires C, 73·17; H, 7·32%; M^+, 246).

1,2,3,4,4a(βH)-tetrahydro-$\Delta^{9,9a}$-7-methoxyfluorene-2-carboxylic acid (77).

The reaction was performed under the dehydration conditions specified by House[33]. The hydroxy-acid (37a) (500mg; 1·90mmol) was disolved in anhydrous benzene (150ml) and p-toluenesulphonic acid (40mg) was added and the resulting solution was refluxed for 3 hours under a nitrogen atmosphere, with the continual removal of water. The solution was cooled to room temperature and diluted with ethyl acetate (100ml). The solution was washed with water and brine, dried and concentrated to afford a micro-crystalline solid. Recrystallisation from chloroform-hexane gave colourless needles of pure olefinic acid (77) (0·42g; 91%), m.p. 187·5-188·5°, νmax. (KBr) 1700cm^{-1} (acid C=O) and 1620, 1610,1580 cm^{-1} (C=C), λmax. 208 nm (ϵ 2,730), 251 nm (ϵ 6,980), 256 nm (ϵ 7,500), 262 nm (ϵ 5,540) and 329 nm (ϵ 1,410), δ 10·70 (1H,s,COOH), 7·26 (1H,d,J=9Hz, aryl-5-H), 6·84 (1H,d,J=2Hz,aryl-8-H), 6·68 (1H,q,J=9,2Hz,aryl-6-H), 6·42 (1H,s,olefinic H), 3·82 (3H,s,OMe), 3·36 (1H,m, benzylic H) and 3·2-1·0 (7H,m,aliphatic H) (Found: C, 73·46; H, 6·85%; M^+, 244. $C_{15}H_{16}O_3$ requires C, 73·76; H, 6·57%; M^+, 244).

1,2,3,4-tetrahydro-7-methoxyfluorene-2-carboxylic acid (62).

The isomerisation conditions employed were those used by House[33] in the isomerisation of 1,2,3,4,4a(βH)-tetrahydro-$\Delta^{9,9a}$-7-methoxyfluorene. The olefinic acid (77)

(700mg; 2·87mmol) was disolved in ethanol (15ml) and sodium hydroxide (0·23g; 6mmol) was added and the resulting solution was stirred under a nitrogen atmosphere at 40° for 2 hours. The solution was then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford solid, isomeric olefinic acid. Recrystallisation from ethyl acetate-petrol gave colourless needles of olefinic acid (62) (658mg; 94%), m.p. 186-194°. Column chromatography on silica gel (300g) eluted with petrol (60-80)-ethyl acetate-acetic acid (84·5-15-0·5 : 74·5-25-0·5) afforded two fractions. Recrystallisation from ethyl acetate-petrol of one fraction gave long needles of olefinic acid (62) (49mg), m.p. 208·5-209·5° (lit. 213° [43] and 205-209° [2]), ν max (Nujol) 1700 cm^{-1} (acid C=O) and 1610, 1580cm^{-1} (C=C), λ max. 225, 257, 267 nm, δ 10·1 (1H,s,COOH), 7·2-6·7 (3H,m,aryl H), 3·80 (3H,s,OMe), 3·3 (2H,m,benzylic H) and 2·8-1·1 (7H,m,aliphatic H) (Found: M^+, 244. $C_{15}H_{16}O_3$ requires M^+, 244).

The other compound isolated from the column was recrystallised from ethyl acetate-petrol to afford an unidentifiable, crystalline solid (6mg), m.p. 203-205°, ν max. (Nujol) 1700 cm^{-1}, 1610, 1580 cm^{-1}, λ max. 226, 257, 266 nm. M^+, 300.

Hydrogenation of 1,2,3,4-tetrahydro-7-methoxyfluorene-2-carboxylic acid (62).

The olefinic acid (62) (40mg; 0·164mmol) was stirred in a suspension of ethyl acetate (25ml) and Adam's catalyst (1mg) under a hydrogen atmosphere at room temperature and pressure for 1 hour. Removal of the solvent and catalyst afforded a white powder which, on recrystallisation from chloroform, afforded the acid (71) (37mg) m.p. 164-166°, similar in all respects but melting point to authentic acid (71) (m.p. 170-171°). Analysis of the acid gave the following data: ν max. (CCl_4) 1691 cm^{-1}

(acid C=O), δ 10·01 (1H,s,COOH), 7·21 (1H,d,J=9Hz,aryl-5-H), 6·84 (1H,d,J=2Hz,aryl-8-H), 6·58 (1H,q,J=9,2Hz,aryl-6-H), 3·76 (3H,s,OMe) and 3·4-1·0 (11H,m,aliphatic H). A mixed melting point of the two acids afforded 158-164°.

1,2,3,4,4a(βH),9a(βH)-hexahydro-2-diazoacetyl-7-methoxyfluorene (7a).

The acid (71) (3·78g; 15·36mmol) was stirred in a solution composed of oxalyl chloride (4ml), ether(12ml) and pyridine (4 drops) for 2 hours. The solution was filtered and evaporated to afford a clear oil. On addition of ether (10ml) and re-evaporation of the solution, a white powder was formed. Recrystallisation from methylene chloride-hexane gave colourless needles of pure acid chloride (72) (3·98g; 95%), m.p. 156-157°, ν max. (Nujol) 1810 cm^{-1} (acid chloride C=O), δ 7·41 (1H,d,J=9Hz,aryl-5-H), 7·24 (1H,d, J=2Hz,aryl-8-H), 6·85 (1H,q,J=9,2Hz,aryl-6-H), 3·77 (3H, s,OMe), 3·57 (1H,m,benzylic H) and 3·2-1·4 (10H,m,aliphatic H) (Found: C, 68.11; H, 6·49%; M^+, 264,266 (3:1). $C_{15}H_{17}O_2Cl$ requires C, 68·05; H, 6·42%; M^+, 264·5).

To a stirred solution of ice-cold ethereal diazomethane was added a solution of the acid chloride (72) (3.98g as prepared above) in anhydrous benzene (15ml) dropwise over 30 minutes. Stirring was continued at 0° for a further 3 hours and then at room temperature overnight. The solution was evaporated by a water pump at room temperature while vigorously stirred, to afford crude diazo ketone (7a). Recrystallisation from methylene chloride-petrol (60-80) gave long, colourless needles of pure diazo ketone (7a) (2·85g; 69% based on the acid (71)), m.p. 111-112°, ν max. (CCl_4) 2100 cm^{-1} ($C=N^+=N^-$), 1630 cm^{-1} (C=O of $COCHN_2$) and 1600, 1580 cm^{-1} (C=C), λ max. 222 nm (ε 8,010), 276 nm (ε 2,100) and 283 nm (ε 1,850), δ 7·37 (1H,d,J=9Hz, aryl-5-H), 6·99 (1H,d,J=2Hz,aryl-8-H), 6·64 (1H,q,J=9,2Hz, aryl-6-H), 5·38 (1H,s,$COC\underline{H}N_2$), 3·77 (3H,s,OMe) and 3·0-1·0 (11H,m,aliphatic H) (Found: M^+, 270. $C_{16}H_{18}O_2N_2$ requires

M^+, 270). The diazo ketone (7a) proved too unstable for elemental analysis and polymerised into an unidentifiable compound unless stored in an opaque container under an inert atmosphere.

1,2,3,4,4a(βH),9a(βH)-hexahydro-2-diazoacetyl-9α-hydroxy-7-methoxyfluorene (76).

A suspension of the hydroxy-acid (37a) (2·05g; 7·8mmol) in a solution composed of oxalyl chloride (2ml; 24mmol), ether (5ml) and pyridine (4 drops) was stirred for 3 hours under a nitrogen atmosphere. The solution was filtered, evaporated and ether (15ml) was added to the resultant clear oil. On re-evaporation a white powder formed (75) max. (Nujol) 1795 cm^{-1} (acid chloride C=O).

Without isolating the crude acid chloride (75) it was disolved in anhydrous benzene (20ml) and the resulting solution was added dropwise to a solution of ethereal diazomethane (excess) containing triethylamine (1ml) in an ice bath. The solution was stirred for a further 5 hours at 0^o and overnight at room temperature. The solution was filtered and evaporated to afford a crude, yellowish solid. A double recrystallisation from methylene chloride afforded colourless needles of the hydroxy-diazo ketone (76) (1·07g; 48%), m.p. 124-126°, ν max. (Nujol) 2100 cm^{-1} ($C=N^+=N^-$), 1640 cm^{-1} (C=O of $COCHN_2$), λ max. 223 nm (ε 14,100), 277 nm (ε 7,400) and 325 nm (ε 3,170), δ 7·38 (1H,d,J=9Hz,aryl-5-H), 6·98 (1H,d,J=2Hz.aryl-8-H), 6·64 (1H,q,J=9,2Hz,aryl-6-H), 5·49 (1H,s,$CO\underline{C}HN_2$), 5·20 (1H.d,J=5Hz,α-hydroxybenzylic H), 3·71 (3H,s,OMe), 3·20 (1H,m,benzylic H), 3·15 (1H,s,ROH) and 2·6-1·0 (8H,m,aliphatic H) (Found: C, 67·4; H, 6·39%. $C_{16}H_{18}O_3N_2$ requires C, 67·17; H, 6·29%).

1,2,3,4,4a(βH)-tetrahydro-$\Delta^{9,9a}$-2-diazoacetyl-7-methoxyfluorene (8a).

A solution composed of the olefinic acid (77)

(3·42g; 14·0mmol), oxalyl chloride (4ml; 48mmol), ether (10ml) and pyiridine (4 drops) was stirred at room temperature under a nitrogen atmosphere for three hours. The solution was filtered, evaporated and re-evaporated on the addition of ether (20ml) to afford a white powder; the acid chloride (89) ν max.(Nujol) 1797 cm^{-1} (acid chloride C=O).

To a stirred solution of excess, ice-cold diazomethane was added a solution of the acid chloride (89) in anhydrous benzene (15ml) dropwise over 30 minutes. Stirring was continued at 0^{o} for a further 3 hours and overnight at room temperature. The solution was filtered and evaporated to afford a yellowish solid. Recrystallisation from methylene chloride afforded pure diazo ketone (8a)(2·43g; 65%), m.p. 121-122^{o}, ν max. (Nujol) 2100 cm^{-1} ($C=N^{+}=N^{-}$), 1637 cm^{-1} (C=O of $COCHN_2$) and 1620, 1610, 1580 cm^{-1} (C=C), λ max. 207 nm (ϵ 2,120), 250 nm (ϵ 6,300), 256 nm (ϵ 7,300) and 327 nm (ϵ 1,410), δ 7·20 (1H,d,J=9Hz,aryl-5-H), 6·92 (1H,d,J=2Hz,aryl-8-H), 6·58 (1H,q,J=9,2Hz,aryl-6-H), 6·39 1H,s,olefinic H), 5·38 (1H,s,$COC\underline{H}N_2$), 3·75 (3H,s.OMe) and 3·2-1·1 (8H,m,aliphatic H) (Found: M^{+}, 268. $C_{16}H_{16}O_2N_2$ requires M^{+}, 268). The diazo ketone proved too unstable for elemental analysis and polymerised unless stored in an opaque container under an inert atmosphere.

Attempted cyclisation of the diazo ketone (76).

To a vigorously stirred suspension of dry cyclohexane (400ml) and cuprous oxide (1·5g) refluxing under a 350 watt tungsten lamp[50] was added a solution of the diazo ketone (76) (100mg) in anhydrous cyclohexane (250ml) dropwise over 1 hour. The resulting suspension was stirred under reflux overnight, filtered and evaporated to yield a brown solid. Column chromatography of the reaction product on silica gel (100g) eluted with ethyl acetate-hexane (25:75) afforded an unresolvable, brown oil (3mg) composed of 3 compounds. The remaining material remained at

the head of the column and proved to be polymeric (mass spectrometry). Analusis of the oil gave the following data: νmax. (CCl_4) 1733 cm^{-1}, λmax. 223 nm, M^+, 500,480,460,433.

Variation of the reaction time (4-48 hours), volume of solvent (100-1000ml), type of solvent (cyclohexane, carbon tetrachloride, hexane, n-pentane and toluene), amount of catalyst (0·1-5g) and atmosphere (air, nitrogen and argon) for similar reactions of the diazo ketone (76) (100mg) did not improve the reaction significantly.

Attempted cyclisation of the diazo ketone (7a).[50]

Yoshikoshi's conditions for the cyclisation of the diazo ketone (73) into the ketone (74) were employed. To a vigorously stirred suspension of anhydrous cyclohexane (350ml) and cuprous oxide (2g) refluxing under a 400 watt photographic lamp was added over 40 minutes a solution of the diazo ketone (7a)(0·5g; 1·85mmol) in dry cyclohexane (500ml). The resulting suspension was stirred under reflux overnight, filtered and evaporated to leave a crude, semi-solid, orange mass. Column chromatography on silica gel (150g) eluted with chloroform-hexane (15:85) isolated a complex mixture of 3 oils (79mg) of almost identical R.f. values which proved inseparable. On variation of the reaction conditions as for the attempted cyclisation of the diazo ketone (76) no greater success was attained. Analysis of the oil afforded the following data: νmax. (CCl_4) 1280, 1580, 1602, 1730 and 2950 cm^{-1}, λmax. 207, 274, 283 nm, δ 7·7-7·3 (m,aryl H),4·0 (t,OMe-3 singlets) and 2·8-0.6 (m, aliphatic H) in the ratio 3:3:22, M^+, 440, 406 and 378, positive D.N.P. test, negative Lassaigne test for nitrogen. Significantly, there were no peaks in the mass spectrum corresponding to the tetracyclic ketone (9); M^+, 242, or the corresponding (hexahydro-7-methoxyfluorene) hydroxymethyl ketone; M^+, 260.

3-methoxy-16-oxogibba-1(10),2,4,9(11)-tetraene (10).

The method employed was based upon the scheme devised by Ghatak[39;40,41,42,43]. A solution of the olefinic acid (77) (168mg; 0·688mmol) in anhydrous methylene chloride (40ml) was added dropwise, with stirring, to a solution of oxalyl chloride (5ml), anhydrous methylene chloride (40ml) and pyridine (4 drops) at 0°. The solution was then stirred at room temperature until no further evolution of hydrogen chloride was detected (2·5 hours). The solution was filtered and the solvent and unreacted oxalyl chloride removed under reduced pressure.The crude acid chloride was dissolved in anhydrous methylene chloride (20ml) and re-evaporated to afford the acid chloride (89) as a white powder, $\nu_{max.}$ (Nujol) 1797 cm^{-1}.

The crude acid chloride (89) was disolved in dry methylene chloride (50ml) and added slowly (1 hour), while stirring, to a solution of excess ethereal diazomethane (10-fold) protected from the light and cooled by an ice bath. Stirring was continued for a further 2 hours at room temperature, whereupon the solvent and excess diazomethane were removed under reduced pressure at room temperature to afford the crude diazo ketone (8a) $\nu_{max.}$ (Nujol) 2110 and 1637 cm^{-1}, as a yellowish solid. The crude diazo ketone (8a) was vacuum dried in a silica gel desiccator for 30 minutes, and, without any further purification, was disolved in dry methylene chloride (100ml) and stirred at -15° in an isopropanol-drikold bath under a nitrogen atmosphere. To this solution was slowly added over 30 minutes a solution composed of anhydrous methylene chloride (100ml) and boron trifluoride etherate (1ml of 48% w/w) while stirring was continued at -15° for a further 45 minutes. The solution was allowed to warm to room temperature and water (15ml) added while stirring was continued for a further 10 minutes. The reaction was diluted with brine and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford an orange gum. The gum was chromatographed on a preparative plate developed in chloroform to give the crude, oily ketone (10) (45mg). The

oil was refrigerated overnight and afforded a white solid which on recrystallisation from ethyl acetate-hexane gave pure olefinic ketone (10) (37mg; 23%), m.p. 124-125° (lit. 124-125° [2] and 128° [43]), ν max. (CCl_4) 1735 cm^{-1} (ketone C=O), λmax. 265 nm (ϵ 19,000), δ 7·25 (1H,d,J=9Hz,aryl-5-H), 6·91 (1H,d,J=2Hz,aryl-8-H), 6·75 (1H,q,J=9,2Hz,aryl-6-H), 5·58 (1H,m,olefinic H), 3·80 (3H,s,OMe), 3·00 (2H,broadish s, benzylic H), 2·11 (2H,broadish s,$-CH_2CO-$) and 3·0-1·4 (9H,m, aliphatic H) (Found: C, 79·9; H, 6·76%. $C_{16}H_{16}O_2$ requires C, 79·97; H, 6.71%).

Attempted cyclisation of the diazo ketone (8a) to the tetracyclic ketone (10).

a) Cuprous oxide as initiator.

To a vigorously stirred suspension of cuprous oxide (1g) in anhydrous cyclohexane (400ml), refluxing under a 400 watt lamp, was added over 30 minutes, a solution of the diazo ketone (8a) (0·5g; 1·40mmol) in anhydrous cyclohexane (450ml), as prescribed by Yoshikoshi[50]. The resulting suspension was stirred under reflux overnight, filtered and evaporated to afford a gummy, red semi-solid, which refused to crystallise. Column chromatography on silica gel (210g) eluted with chloroform-hexane (10:90 - 15:85) isolated only polymeric material (by mass spectrometry), leaving a complex mixture of at least four compounds (15mg), all of which were less polar than the keto-olefin (10) as indicated by a thin layer chromoplate developed in ether-hexane (15:85).

Variation of the solvent, time of reaction, amount of reactants and reaction atmosphere, in a similar manner to the diazo ketone (76), resulted in no greater success.

b) Trifluoroacetic acid as initiator[2].

A solution of the diazo ketone (8a) (200mg) in

anhydrous methylene chloride (2ml) was added dropwise to a vigorously stirred solution of trifluoroacetic acid (10ml) and methylene chloride (10ml) at -20° under a nitrogen atmosphere. The solution was allowed to warm to room temperature and stirring was continued for a further hour. The solution was then quenched with water (20ml) and extracted with methylene chloride. The organic phase was washed with brine, dried and concentrated to afford a red gum which was chromatographed on a preparative plate developed in ether-hexane (25:75) to give the identical complex oil (46mg) produced in a). Analysis of the oil gave the following data: ν max. (CCl_4) 1580, 1602, 1620, 1730 and 2940 cm^{-1}, λ max. 208, 275 and 282 nm, δ (CCl_4) 7·8-7·4 (aryl H), 7·1-6·9 (olefinic or aryl H), 4·0 (OMe) and 3·7-1·0 (aliphatic H) in the ratio (3:3:2:28), M^+, 500, 460 and 438, positive D.N.P. test and negative Lassaigne test for nitrogen.

3-methoxybenzoic acid.

3-hydroxybenzoic acid was methylated in a similar manner as that used by Bachmann[79]. 3-hydroxybenzoic acid (69g; 0·5mol) was placed in a 1000ml flask and a cold solution of 2M sodium hydroxide (500ml) was added and the flask tightly stoppered to prevent the oxidation of the phenol, and shaken until all of the acid had disolved. Dimethyl sulphate (89g; 0·71mol) was quickly added and the flask was shaken for 20 minutes and cooled in a cold water bath to keep the reaction temperature below 35° while occasionally vented. A second portion of dimethyl sulphate (89g) was added and shaking was continued for 10 minutes more. The solution was then cooled and acidified with dilute hydrochloric acid and the precipitate of 3-methoxybenzoic acid filtered off and washed with brine. Recrystallisation from hot water gave pure acid (64g; 84%), m.p. 107-108° (lit.[80] 107-108°), ν max. (KBr) 1695 cm^{-1} (acid C=O), λ max. 219 nm (ϵ 5,700) and 231 nm (ϵ 6,700) (Found: M^+, 152. $C_8H_8O_3$

requires M^+, 152).

2-bromo-5-methoxybenzoic acid.

This was prepared as described in the literature[79] by the reaction of the calculated amount of bromine introduced slowly beneath the surface of a hot, aqueous solution of 3-methoxybenzoic acid to produce colourless crystals of the desired bromo-acid, m.p. 160·5-161·5° (lit[79]. 161-162°), νmax. (KBr) 1700 cm^{-1} (acid C=O), δ (D_3CCOCD_3) 10·42 (1H,s,COOH), 7·42 (1H,d,J=9Hz,aryl-3-H), 7·10 (1H,d, J=2Hz,aryl-6-H), 6·71 (1H,q,J=9,2Hz,aryl-4-H) and 3·82 (3H,s, OMe) (Found: M^+, 230,232 (1:1 ratio). $C_8H_7O_3Br$ requires M^+, 231).

2-bromo-5-methoxybenzyl alcohol (81).

2-bromo-5-methoxybenzoic acid (60g; 0·26mol) was disolved in anhydrous ether (1500ml) and added dropwise to a stirred suspension of lithium aluminium hydride (10g; 0·26mol) in dry ether (500ml) at room temperature under a nitrogen atmosphere in the manner developed by Adam[81]. The suspension was stirred for a further 2 hours, cooled on an ice bath and slowly acidified with cold, dilute sulphuric acid. The solution was successively washed with aqueous sodium bicarbonate, water and brine, dried and concentrated to afford crystalline benzyl alcohol (81). Recrystallisation from ether-petrol afforded long, colourless needles of pure alcohol (81) (51·2g; 91%), m.p. 45-46° (lit[79]. 46°), νmax. (CCl_4) 1593 cm^{-1} (C=C) and 3641 cm^{-1} (benzyl alcohol), δ 7·40 (1H,d,J=9Hz,aryl-3-H), 7·08 (1H,d,J=2Hz,aryl-6-H), 6·68 (1H,q,J=9,2Hz,aryl-4-H), 4·68 (2H,s,benzylic H), 3·79 (3H,s,OMe) and 2·95 (1H,s,ROH) (Found: C, 44·50; H, 4·18%; M^+, 216,218 (1:1 ratio). $C_8H_9O_2Br$ requires C, 44·24: H, 4·15%; M^+, 217).

1-(2-bromo-5-methoxybenzyloxy)-1-ethoxyethane (85).

A solution of the benzyl alcohol (81) (20·8g; 0·096mol) in anhydrous ether (100ml), ethyl vinyl ether (6.88g; 1·5 equivalents) and concentrated hydrochloric acid (1 drop) was stoppered and shaken at room temperature for 4 hours. Dilute sodium hydroxide was added and an extra batch of ether (100ml) added, and the solution was washed with brine, dried and concentrated to afford a colourless liquid acetal (85) (2·72g; 98·2%), b.p. 97-98·5° (0·05 mm), νmax. (CCl_4) 1135 cm^{-1} (C-O-C), 1595 cm^{-1} (C=C) and 2980 cm^{-1} (aliphatic C-H), λmax. 229 nm (ϵ 7,940) and 281 nm (ϵ 1,070), δ (CCl_4) 7·38 (1H,d,J=9Hz,aryl-3-H), 7·2-6·6 (2H,m,aryl H), 4·81 (1H,q,J=7Hz,acetal H), 4·61 (2H,s,benzylic H), 3·79 (3H,s,OMe), 3·59 (2H,q,J=7Hz,-$OC\underline{H}_2Me$), 1·33 (3H,d,J=7Hz, acetal CH_3) and 1·22 (3H,d,J=7Hz,-$OCH_2C\underline{H}_3$) (Found: C, 50·02; H, 6·16%; M^+, 288,290 (1:1 ratio). $C_{12}H_{17}O_3Br$ requires C, 49·82; H, 5·89%; M^+, 289).

Hyrolysis of the acetal (85).

The acetal (85) (1·42g; 5mmol) was disolved in a solution composed of ethanol (50ml), water (10ml) and concentrated sulphuric acid (1 drop) and warmed at 60° for 3 hours. Ethyl acetate (100ml) was added and the resultant solution was washed with brine, dried and concentrated to afford a crystalline solid. Recrystallisation from ether-petrol gave pure benzyl alcohol (81) (0·96g; 88·5%), m.p. 45-46° (lit[79]. 46°), as long, colourless needles.

Attempted conversion of the alcohol (81) to 1,2,3,4-hexahydro-7-methoxyfluorene.

The reaction was performed under the conditions stated by the late Parham[54]. Dry alcohol (81) (8·0g; 37mmol)

was added to a flame dried round bottom flask equipped with an addition funnel, alcohol thermometer and nitrogen inlet. Dry tetrahydrofuran (50ml), freshly distilled from lithium aluminium hydride, and sodium dried hexane (10ml) were added and the solution cooled to -15° in a drikold-isopropanol bath under a positive nitrogen pressure. n-butyllithium (80mmol) in hexane (20ml) was added slowly over 1 hour at -15° and formed a thick, white precipitate, while stirring was continued for an additional 2 hours at -10 to -15°. Cyclohexanone (5·0g; 50mmol) in hexane (25ml) was added to the cold slurry over 30 minutes while maintaining the temperature at -15° and stirring was continued for a further 2 hours whereupon the mixture was allowed to warm to room temperature and stirred under a nitrogen atmosphere for an extra 20 hours. The reaction solution was hydrolysed by saturated, aqueous ammonium chloride (80ml) and the two phases were separated. The aqueous layer was extracted with ethyl acetate (2 x 100ml) and the combined organic extracts were washed with brine, dried and concentrated to afford a yellow oil. High vacuum distillation of the oil left a residual yellow solid which on recrystallisation from ether-petrol gave pure benzyl alcohol (81) (6·8g), m.p. 45-46°. The fractionally distilled liquid was composed of cyclohexanone (4·4ml) and m-methoxybenzyl alcohol (82) (0·68g), b.p. 250-252° (lit[80]. 252°).

5-methoxy-2-methylbenzyl alcohol (83).

A solution of the alcohol (81) (2·17g; 10mmol) in anhydrous cyclohexane (3ml) and dry tetrahydrofuran (10ml) was stirred under a nitrogen atmosphere at -15° and n-butyllithium (22mmol) in dry cyclohexane (10ml) was added over 30 minutes and stirred for a further 2 hours at -15°. Methyl iodide (1·56g; 11mmol) in cyclohexane (4ml) was added over 10 minutes and the solution was stirred for a further 2 hours at -15° and then at room temperature for 20 hours.

On work up as before a yellowish oil was formed. This was distilled to produce a yellowish solid residue and a colourless oil. On recrystallisation from ether-petrol pure alcohol (81) (1·75g), m.p. 45-46°, was formed. Chromatography of the oil on a preparative plate developed in petrol-ether (80:20) produced two fractions: the expected 5-methoxy-2-methylbenzyl alcohol (83) (48mg; 3·2%),b.p. 111-113° (0·8mm) (lit. 104-106° at 0·6mm[83] and 136° at 8mm[82]), δ 7·38 (1H,d,J=9Hz,aryl-3-H),7·04 (1H,d,J=2Hz,aryl-6-H), 6·68 (1H,q,J=9,2Hz,aryl-4-H), 4·67 (2H,s,benzylic H), 3·80 (3H,s,OMe), 2·95 (1H,s,ROH) and 2·21 (3H,s,Me) (Found: M^+, 152. $C_9H_{12}O_2$ requires M^+, 152).

The other product from the preparative plate was m-methoxybenzyl alcohol (82)(0·38g), b.p. 250-251° (lit[80]. 252°).

Attempted conversion of 2-bromo-5-methoxybenzyl alcohol (81)and acetone to 2-(4-methoxy-2-benzyl alcohol)-propan-2-ol.

A solution of the alcohol (81) (4·34g; 20mmol) in dry cyclohexane (8ml) and tetrahydrofuran (25ml) was stirred under a nitrogen atmosphere at -15° and n-butyllithium (44mmol) in cyclohexane (15ml) was added over 20 minutes. Anhydrous acetone (1·5g; 25mmol) in cyclohexane (5ml) was added over 15 minutes and the mixture stirred for a further 2 hours at -15° and then at room temperature for 20 hours. On work up as before, a yellow oil was produced which was composed of starting material (81) (3·6g), m.p.45-46°, and m-methoxybenzyl alcohol (82) (365mg), b.p. 250-252°.

Reaction of the acetal (85) with acetone and n-butyllithium.

A solution of the acetal (85) (7·1g; 25mmol) in anhydrous cyclohexane (10ml) and tetrahydrofuran (20ml) was stirred at -15° under a nitrogen atmosphere for 3 hours and a solution of n-butyllithium (55mmol) in dry cyclohexane

(15ml) was added over 30 minutes and stirring was continued for a further 4 hours. Dry acetone (1·74g; 30mmol) in dry cyclohexane (10ml) was added over 30 minutes and stirring was continued at -15° for 3 hours more and then at room temperature for 20 hours. On the usual work up , the only products were starting material (85) (5·43g) and debrominated acetal (87) (0·6g), b.p. 85-87° (0·1mm) separable from column chromatography on silica gel (150g) eluted with petrol (60-80)-ether (90:10).

1-(m-methoxybenzyloxy)-1-ethoxyethane (87) gave the following data: ν max. (CCl_4) 1135 cm^{-1} (C-O-C), 1600cm^{-1} (C=C) and 2950 cm^{-1} (aliphatic C-H), λ max. 223 nm (ϵ 12,100) and 230 nm (ϵ 10,800), δ (CCl_4) 7·42-6·73 (4H,m,aryl H), 4·80 (1H,q,J=7·2Hz,acetal H), 4·56 (2H,s,benzylic H), 3·74 (3H,s,OMe), 3·58 (2H,q,J=7·2Hz,-$OC\underline{H}_2Me$), 1·32 (3H,d,J=7·2Hz, acetal CH_3) and 1·18 (3H,d,J=7·2Hz,-$OCH_2C\underline{H}_3$) (Found: C, 68·39; H, 8·57%; M^+, 210. $C_{12}H_{18}O_3$ requires C, 68·54; H, 8·57%; M^+, 210).

Reaction of the acetal (85) with methyl iodide and n-butyllithium.

A solution of the acetal (85) (7·1g; 25mmol) in anhydrous cyclohexane (10ml) and dry tetrahydrofuran (20ml) was stirred at -15° under a nitrogen atmosphere and n-butyllithium (55mmol) in dry cyclohexane (12ml) was added over 30 minutes and stirring was continued at -15° for a further 3 hours. Methyl iodide (4·26g; 30mmol) in dry cyclohexane (10ml) was added over 30 minutes and stirred at -15° for a further 3 hours and then at room temperature for 20 hours. On the usual work up, the only products isolated were starting material (85) (5·62g), b.p. 97-98·5° (0·05mm) and debrominated acetal (87) (0·58g), b.p. 84-87°(0·1mm); distilled separately after purification by column chromatography.

Grignard reactions of the acetal (85).

a) With cyclohexanone.

A mixture of the acetal (85) (5·69g; 20mmol), magnesium filings (prewashed in ether and dried at 100° under vacuum) (0·5g; 22mmol) and dry tetrahydrofuran (125ml) was refluxed under a nitrogen atmosphere for 3 hours until almost all of the magnesium had reacted, and the reaction mixture was filtered. Anhydrous cyclohexanone (8ml) in dry tetrahydrofuran (10ml) was added over 15 minutes and the resulting solution was refluxed overnight. The mixture was cooled to room temperature, poured onto crushed ice, acidified with cold, dilute sulphuric acid and extracted with ether. The organic phase was washed with brine, dried and concentrated to afford a yellowish oil composed of two liquids separable by fractional distillation: cyclohexanone (7·6ml) and the acetal (87) (3·85g), b.p. 85-86·5° (0·1mm).

b) With solid carbon dioxide.

A mixture of the acetal (85) (2·84g; 10mmol), magnesium filings, purified as in a), (0·25g; 11mmol) and dry tetrahydrofuran (70ml) was refluxed for 3 hours under a nitrogen atmosphere and filtered. The cold Grignard solution was poured onto drikold (15g), in the form of small lumps, very slowly while the resulting mixture was stirred. Stirring was continued until all the drikold had disappeared. On work up as in a), a clear, colourless liquid was obtained. On distillation, pure debrominated acetal (37) (2·05g; 93%), b.p. 85-86° (0·1mm) was the sole product.

c) With cyclohexanone in the presence of magnesium bromide.

A mixture of the acetal (85) (1·42g; 5mmol), magnesium filings, purified as in a), (0·126g; 5·5mmol) and dry tetrahydrofuran (50ml) was refluxed for 3 hours under a nitrogen atmosphere and filtered. Anhydrous magnesium bromide (0·92g; 5mmol), as prescribed by Meyers[57], was added to the Grignard reagent and cyclohexanone (2ml) in anhydrous tetrahydrofuran (10ml) was added over 15 minutes at room

temperature and then refluxed overnight. On the usual work up and fractional distillation, pure cyclohexanone (1·8ml) and m-methoxybenzyl alcohol (82) (0·73g; 96%), b.p. 251-252°, δ (CCl_4) 7·21-6·62 (4H,m,aryl H), 4·58 (2H,s,benzylic H), 3·74 (3H,s,OMe) and 2·60 (1H,s,ROH) were obtained.

d) With acetone in the presence of magnesium bromide.

The Grignard reagent, as prepared in c), (5mmol) had dry magnesium bromide (0·92g; 5mmol) and dry acetone (2ml) added and refluxed overnight under a nitrogen atmosphere. On the usual work up, pure m-methoxybenzyl alcohol (82) (0·74g; 97%), b.p. 250-252°, was the sole product.

Attempted Grignard reaction of the alcohol (81).

A solution of the alcohol (81) (14·45g; 50mmol) in dry tetrahydrofuran (100ml) was added dropwise to a suspension of resublimed magnesium (1·34g; 55mmol) in dry tetrahydrofuran (15ml) and methyl iodide (2 drops) under a nitrogen atmosphere, and the suspension was refluxed overnight to afford a white precipitate which proved to be the salt of the alcohol (81) by acidification with dilute hydrochloric acid, extraction with ether, washing the organic phase with brine, drying and concentration to produce a colourless oil which recrystallised from ether-petrol to afford pure benzyl alcohol (81) (7·9g), m.p. 45-46°. The distillate of the mother liquor revealed the presence of m-methoxybenzyl alcohol (82), b.p. 250-252°.

1-carboxy-2-(p-methoxyphenyl)-cyclohex-4-enyl acetic acid anhydrides (32a), (32b) and (32c).

This was prepared as a three component, stereoisomeric mixture, as described in the literature[20], by the reaction between an intimate mixture of powdered

5-(p-methoxyphenyl)-trans,trans-penta-2,4-dienoic acid (13) (10g; 46mmol) and itaconic acid (13g; 0·1mol) heated under a nitrogen atmosphere for 9 hours at 156°, ν max. (film) 1845, 1770 cm^{-1} (anhydride).

Attempted preparation of 3-methoxy-6,16-dioxo-9(βH)-gibba-$\Delta^{11,12}$-A-tetraene (31) - Isolation of methyl 1,4,4a,9,10,10a-hexahydro-7-methoxy-9-oxophenanthrene-10a-carboxylate (34).

The mixture of anhydrides (32a,b,c) (10g; 37mmol) was added to polyphosphoric acid[67] (137·5g), and the syrupy mixture was stirred at 80° for 30 minutes, cooled, poured onto crushed ice and stirred for 1 hour. Cold, dilute hydrochloric acid was added and the aqueous solution was then stirred for 15 minutes more and extracted with chloroform. The organic phase was washed with water and brine, dried and concentrated to afford a brown gum (9·6g), which contained numerous components, all of which were acidic since the gum was completely soluble in aqueous sodium carbonate.

The gum (5g), in dry methanol (100ml) and 98% sulphuric acid (0·5ml), was refluxed for 4 hours, cooled and extracted with methylene chloride. The solution was washed with water and brine, dried and concentrated to afford a tan coloured oil containing at least 5 constituents. Silica gel (300g) chromatography of the oil, eluted with chloroform-hexane (5:95), afforded only one isolable component; the keto-ester (34). Recrystallisation from methylene chloride gave the pure ester (34) (0·39g; 7·4% based on the initial anhydrides (32a,b,c)), m.p. 184-185°, as a single isomer, νmax. (KBr) 1729 cm^{-1} (ester C=O) and 1682 cm^{-1} (ketone C=O characteristic of a phenanthrenone), λ max. 224 nm (ϵ 6,900), 253 nm (ϵ 3,130) and 319 nm (ϵ 1,180), δ 7·90 (1H,d,aryl-5-H), 6·81 (2H,m,aryl H), 5·42 (2H,m,olefinic H), 3·92 (1H,m, benzylic H), 3·80 (3H,s,OMe), 3·62 (3H,s,OMe), 2·81 (2H,s, $-CH_2CO-$) and 2·25-1·94 (4H,m,aliphatic H) (Found: C, 70·20; H, 6·47%. $C_{17}H_{18}O_4$ requires C, 70·32; H, 6·30%).

Methylation of the gum with a solution of excess

ethereal diazomethane, followed by chromatographic separation as above, afforded the same ester (34) (0.41g from 4g of gum; 9·7% based on the anhydrides (32a,b,c)), m.p. 184-185°, after recrystallisation from methylene chloride.

The corresponding acid (33), m.p. 202-203°, from base hydrolysis of the above methyl ester (34) followed by recrystallisation from chloroform, gave $\nu_{max.}$ (Nujol) 1701, 1681 cm^{-1} (acid and phenanthrenone ketone C=O respectively), $\lambda_{max.}$ 225 nm (ϵ 8,200), 250 nm (ϵ 3,540) and 320 nm (ϵ 1,340), δ 11·42 (1H,s,COOH), 7·92 (1H,d,J=9Hz,aryl-5-H), 6·8 (2H,m, aryl H), 5·39 (2H,m,olefinic H), 3·98 (1H,m,benzylic H), 3·82 (3H,s,OMe), 2·81 (2H,s,$-CH_2CO-$) and 2·2-1·9 (4H,m, aliphatic H) (Found: M^+, 272. $C_{16}H_{16}O_4$ requires M^+, 272). Elemental analysis was obtained on refluxing the acid (33) in anhydrous ethanol in the presence of concentrated hydrochloric acid to afford, after recrystallisation from methylene chloride, the corresponding ethyl ester, m.p. 188-189°, (Found: C, 72·24; H, 6·89%. $C_{18}H_{20}O_4$ requires C, 72·00; H, 6·67%).

Attempted preparation of 1,4,4a,9a-tetrahydro-7-methoxy-9-oxofluorene-9a-acetic acid (30) - Isolation of the keto-ester (34).

To a stirred solution of the anhydrides (32a,b,c) (1·20g; 4·41mmol) in anhydrous methylene chloride (100ml) in an isopropanol-drikold bath at -15°, was added slowly over 2 hours, triply sublimed aluminium chloride (1.65g; 13·2mmol). The suspension was allowed to warm to room temperature and stirring was continued overnight until the evolution of hydrogen chloride had ceased, whereupon the mixture was poured onto crushed ice and extracted with chloroform. The organic phase was washed with brine, dried and concentrated to afford an orange gum which refused to crystallise. The gum was stirred overnight at room temperature in the presence of excess ethereal diazomethane to afford, after the removal of the polymer and solvent,

a tan coloured oil. Chromatography on silica gel (130g), eluted by chloroform-petrol (5:95), afforded the keto-ester (34) as a white solid. Recrystallisation from methylene chloride yielded pure ester (34) (0·27g; 22%),m.p. 184-185°, as a single, but indeterminable, isomer, identical with that produced by the polyphosphoric acid treatment of the anhydrides (32a,b,c).

Formation of the phenanthrenone (34) from the polyphosphoric acid treatment of 1-carboxy-2-(p-methoxyphenyl)-cyclohex-4-en-1-acetic acid (35).

The anhydride mixture (32a,b,c) (10g; 37mmol) was stirred in a warm (40°) solution of 4M sodium hydroxide (100ml) in ethanol (100ml) for 30 minutes, washed with ether, acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to afford white, powdery diacid (35) $\nu_{max.}$ (Nujol) 1696 cm^{-1} (broad) (acid C=O).

Without further purification, the diacid (35) (4·5g; 17mmol) was added to freshly prepared polyphosphoric acid[67] (69g) over 30 minutes at 40°, and the resulting mixture was stirred at 80° for a further 30 minutes. On the previous work up employed on the anhydrides (32a,b,c), followed by esterification with diazomethane ang chromatographic purification, crude ester (34) was obtained. Recrystallisation from methylene chloride afforded pure keto-ester (34) (0·17g; 3·5%), m.p. 184-185·5°, identical with that prepared above.

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